Norwegian drug information centres strongly promote person-centred and personalised medicine: a brief report on the achievements and strategy

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Abstract

The Norwegian network of drug information centres (RELIS) has achievements in person-centred and personalised medicine. RELIS receive questions from physicians, pharmacists, nurses and other health professionals and provide decision support in all aspects of pharmacotherapy. Questions associated with person-centred medicine often include problems with unrealistic risk perception and poor adherence among patients. Questions associated with personalised medicine frequently concern comorbidity, biomarkers and pharmacogenetics. The questions frequently include a mix of problems related to health and disease care. The RELIS staff addresses each question in a problem-oriented approach with expertise in pharmacology and skills in searching and critical evaluation of the literature. A written answer can describe decision support concerning patient empowerment, further diagnostics and preferences in pharmacotherapy including advice with regard to choice of drug and dose to a patient. Links to online resources and attached references for further reading are often included in the answers. The question–answer service is documented in a full-text, searchable question–answer database. Additional drug information activities towards clinicians and patients, and a multi-professional staff with pharmacists and clinical pharmacologists, are important elements in RELIS drug information strategy, and it is essentially relevant to predictive, preventive and personalised medicine (PPPM).

Keywords Database · Decision support · Drug information centre · Multi-professional expertise · Patient empowerment · Person-centred medicine · PPPM · Risk

Abbreviations

ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
CYP	Cytochrome P450
DICs	Drug information centres
DILI	Drug-induced liver injury
ECT	Electroconvulsive therapy
GP	General practitioner
HRT	Hormone replacement therapy
OC	Oral contraceptives
PPPM	Predictive, preventive and personalised medicine

Q / A	Question/answer pairs
RELIS	Norwegian network of drug information centres
SSRIs	Selective serotonin reuptake inhibitors
TCAM	Traditional, complementary and alternative medicine
TDM	Therapeutic drug monitoring

Introduction

The Norwegian network of drug information centres (RELIS) was developed from a model described in the Lancet entitled: “Problem-oriented drug information: a clinical pharmacological service” describing a drug information centre (DIC) run by clinical pharmacologists and pharmacists to provide decision support to hospital and outpatient care [1]. RELIS is independent of the pharmaceutical industry and answer questions concerning complex clinical cases (mainly from physicians) for free with written responses within a requested time

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frame [2–4]. A study found that clinicians rose from 0.16 to 1.85 patient-related questions per patient seen, and many of these concerned drug treatment [5]. Physicians have reported that the complexity of patients' comorbidities and contexts, as well as constantly changing resources, are barriers to pursue clinical questions themselves [6]. The possibility to consult a service that provides decision support in pharmacotherapy has been found valuable in surveys and studies of impact among health professionals in Norway [2, 7, 8].

Person-centred medicine originates from a caring and holistic perspective while personalised medicine is based on a biomedical framework [9–11]. RELIS receive questions associated with person-centred medicine that include information about unrealistic risk perception and poor adherence among patients. Questions associated with personalised medicine frequently concern comorbidity, biomarkers and pharmacogenetics. The questions frequently include a mix of problems related to health and disease care. The RELIS staff addresses each question in a problem-oriented approach with expertise in pharmacology and skills in searching and critical evaluation of the literature. A written answer can describe decision support concerning patient empowerment, further diagnostics and including advice with regard to choice of drug and dose to a patient. Links to online resources and attached references for further reading are often included in the answers.

Appraisal of DICs, including RELIS, is mainly by word of mouth communication and surveys of overall user satisfaction. Efforts to study the impact of this type of communication and decision support systematically are generally lacking within the healthcare service [12–14]. However, the achievements of RELIS in person-centred and personalised medicine are of relevance for predictive, preventive and personalised medicine (PPPM). The concept of PPPM promotes an integrated approach combining advantages of individual bio/medical fields and technologies and consolidating a multi-professional collaboration [11, 15]. The multi-professional collaboration is the core relationship in the interaction between a clinician and RELIS. With a staff of pharmacists, clinical pharmacologists and physicians with training in other relevant disciplines (e.g. general practice, geriatrics and psychiatry), RELIS can include experience from pharmacies, laboratory diagnostics and the clinic in the provision of decision support. Although the interaction between a health professional and RELIS usually concerns individual patients in accordance with the concept of “true personalised medicine” [11], such a service could positively affect care and treatment of patients in the future. This mini review exemplifies RELIS achievements in person-centred and personalised medicine and discusses RELIS strategy in the context of PPPM.

Database

RELIS has developed a full-text, searchable question (Q)–answer (A) database (the RELIS database) to document the activity with the possibility of re-using previous answers [3].

Selected pairs, about two-thirds of all Q/A pairs, are published online (www.relis.no) in Norwegian as open access, freely available to health professionals. Answers considered not having any general interest, or questions that are so specific there is a risk the patient can be identified, are only available for the RELIS staff. Reviews of the RELIS database can be used to identify recurring problems in pharmacotherapy including drug safety questions [16]. Reviews can also be used to address poor and inconsistent drug information in prescribing and dispensing software systems. The RELIS database contained a total of 46,361 indexed Q/A pairs by the end of 2018, compared to 396 Q/A pairs by the end of the first year of RELIS in 1995. RELIS handled about 3200 questions in 2018. The database contains a simple search function where a drug (e.g. escitalopram), category (e.g. pregnancy) or a text word (e.g. worried) is entered. In addition, it contains a more advanced search function with Boolean operators (AND/OR/NOT) to combine simple searches [3]. Figure 1 shows how the RELIS database was used to search for relevant examples of Q/A pairs associated with person-centred and personalised medicine, respectively.

Person-centred medicine

Question about use of escitalopram, bupropion, candesartan and esomeprazole in pregnancy (translated from the RELIS database): “I am a general practitioner with a female patient who after years of trial and error has good clinical effect of a combination of escitalopram 20 mg and bupropion 300 mg per day. She also uses candesartan 4 mg for her migraine, and esomeprazole 40 mg, per day. She is probably pregnant, and very worried if she can continue with bupropion and escitalopram, drugs that she has experienced as beneficial for her.”

Comment

The motivation for this question is strongly based on the physician–patient relationship. The patient is worried and the physician consults RELIS in response to this. The general practitioner (GP) puts the patient at the centre of decisions with respect for her preferences and desires. The results from the consultation with RELIS are of interest to both. Seeing the patients as experts and working alongside professionals to get the best outcome is important in person-centred medicine. Thus, in person-centred medicine, attitude emphasizing support, respect and autonomy is of value [10, 11, 17–19]. Such an attitude is integrated in pregnancy and maternity care in Norway, and consultations within the healthcare service are free of charge. A successful pregnancy is of great importance not only for a woman but also for her partner and family. Midwives and physicians share these values. However, pregnant women,

Fig. 1 A full-text, searchable question (Q)–answer (A) database (the RELIS database) was used to find examples of Q/A pairs (Q/As) in Norwegian associated with person-centred (right) and personalised medicine (left). The retrieved Q/As were found with a simple search function for a drug (e.g. escitalopram), category (e.g. pregnancy) or text word (e.g. worried). The simple searches were then combined with the Boolean operator AND. CYP; Cytochrome P450, RELIS; Norwegian network of drug information centres

as well as many physicians, have unrealistically high perceptions of teratogenic drug effects [20, 21]. This may result in suboptimal treatment of disease and even influence decisions of whether to continue a pregnancy. Product-specific information on this topic is often categorical, and the restrictiveness of the information may itself result in increased perception of teratogenic risk between physicians and their patients [20–22].

The answer to the physician included a discussion of mental disease and pregnancy, in particular risk of not treating more serious depression. Furthermore, it included the recommendation of trying to avoid drug therapy in mild to moderate depression. The answer contained a paragraph for each of the drugs the patient used, with respective descriptions of the current evidence for a particular risk in pregnancy. The paragraphs included descriptions of observational studies and case reports concerning short- and long-time effects in organs (e.g. heart, brain) as well as neonatal adaption (if the drug was continued throughout the pregnancy). In the conclusion, the physician was specifically recommended to withdraw candesartan due to it being contraindicated in the 2nd and 3rd trimesters and advised that the drug should be avoided in the first trimester. The use of antidepressants, like escitalopram and bupropion, should be based on a clear indication based on the controversial evidence of risk in

pregnancy. The answer contained 1891 words and 16 references and was co-signed by two pharmacists.

Personalised medicine

Question about use of antidepressants in postapoplectic epilepsy (translated from the RELIS database): “The patient is a male in his 40s with a previous stroke who used escitalopram 15 mg per day for depression. The drug was discontinued after several generalized tonic-clonic seizures where the patient became unconscious. The condition was diagnosed as a postapoplectic epilepsy. The patient was prescribed levetiracetam 250 mg, two tablets twice daily, but probably only uses 250 mg in the evening. He has been seizure free since the antiepileptic was started. The patient now has depressive symptoms, and asks for an antidepressant. I find that all selective serotonin reuptake inhibitors (SSRIs) can lower the seizure threshold. Does RELIS have any good advice for choice of antidepressant in addition to a previous answer I found in the RELIS database (ref)? I think that a careful attempt with an SSRI can be considered, but the patient should step-up his dose of levetiracetam to at least 250 mg twice a day or perhaps 500 mg twice a day. I will also check the

Interaction Database for Norwegian Clinicians (link) before I start treatment. Question from a physician.”

Comment

The motivation for this question is strongly based on the medical history of the patient. The patient experienced complications probably associated with his previous stroke and probably elicited by escitalopram. This clinical case is complex, and the physician needs decision support with regard to drug selection, drug combinations and dosing. The possibility to tailor drug therapy for this patient based on phenotype, through therapeutic drug monitoring (TDM) and genotyping of cytochrome P450 (CYP) enzymes in addition to other diagnostic measures, is relevant. In general, personalised medicine is understood as a medical approach in which patients are stratified based on their disease subtype, risk, prognosis or treatment response using specialised diagnostic tests. The key idea is to base medical decisions on individual patient characteristics, including molecular and behavioural biomarkers [23–25].

The answer to the physician included a discussion of SSRIs and seizure threshold where RELIS confirms that this category of antidepressants, in general, is associated with a relatively low risk. Then, it follows the paragraph that discusses treatment options including reboxetine and moclobemide and drugs that should be avoided like tricyclic antidepressants and bupropion. The possibility of electroconvulsive therapy (ECT) is discussed and that the depressive symptoms could be an adverse effect of levetiracetam. Lamotrigine and carbamazepine are mentioned as equally good antiepileptic drugs and with antidepressant effects. The next paragraph discusses practical advice such as careful dose escalation, performing TDM and perhaps combines it with genotyping of CYP enzymes essential for metabolism of many drugs. The next paragraph discusses the SSRIs with the highest potential for drug interactions like fluoxetine and paroxetine and provides suggestions with links to recommended drug interaction databases. In the conclusion, RELIS suggests avoiding escitalopram due to the medical history of the patient and choose an alternative antidepressant.

The answer contained 604 words and 5 references and was co-signed by two pharmacists. In the text, three websites are linked, including a web portal for availability of genetic analyses in Norway, and link to two recommended drug interaction databases as mentioned above.

Discussion

The two examples described above show the achievements of RELIS in person-centred and personalised medicine. The female patient is reassured about the possibility of drug therapy

if she wants to go on with her pregnancy, and her physician is updated on the use of antidepressants in pregnancy with regard to other patients. The male patient is receiving a thorough follow-up with regard to his postapopleptic epilepsy and depressive symptoms. His physician is updated on the treatment of combined epilepsy and depression with diagnostic tools in pharmacogenetics and drug interactions, respectively. However, spontaneous questions received by RELIS are not necessarily representative of recurring problems in pharmacotherapy experienced by every physician. The RELIS database described above represents a promising tool to explore drug information issues of general interest. Nearly 15% of the questions to RELIS from health professionals concern drug use in pregnancy [21]. Pregnancy is a physiological condition where maternal and fetal well-being is a motivation for preventive measures for optimal healthcare. Categorical drug information and exaggerated risk perception are challenges in this context as stated above. In a survey, we assessed physicians' evaluation of quality and clinical impact of answers from RELIS with regard to drug use during pregnancy. Notably, we observed that almost one out of ten physicians reported that termination of a pregnancy was avoided by the information provided [7]. This demonstrates a potential for saving the lives of the babies yet to be born and consequently reducing health risks and health costs associated with abortion. The health effect of not terminating a wanted pregnancy is essentially important. Furthermore, the fact that avoiding or discontinuing drug therapy was relatively frequently reported as a clinical impact may suggest a potential for preventing teratogenic effects due to the information provided.

Targeted preventive measures could also involve heredity in subjects or their relatives. The factor V Leiden mutation is currently the most common known hereditary defect predisposing to venous thrombosis [26]. In the RELIS database, 233 Q/A pairs from 1995 to 2018 included the text word “Leiden”. A majority of the Q/A pairs concerned safe use of either oral contraceptives (OC) or hormone replacement therapy (HRT) in females with the risk factor or relatives with the risk factor. Venous thromboembolism not only is associated with serious morbidity and mortality, but it also has major implications for healthcare resource utilization.

PPPM also promotes the laboratory as an “active advising partner” to assist clinical practice in the healthcare service [27]. The clinical pharmacology departments that are associated with the RELIS network do closely cooperate both with the TDM laboratories and with medical biochemistry departments. Thus, questions concerning clinical laboratory values (e.g. biomarkers, pharmacogenetics and drug concentrations) in the context of pharmacotherapy are common. Cases concerning suspected traditional, complementary and alternative medicine (TCAM)-induced or drug-induced liver injury (DILI) in patients with elevated alanine aminotransferase (ALT) and elevated alkaline phosphatase (ALP) are frequent

[28, 29]. In our answers, the relevance of the laboratory values is explained to a clinician motivated to solve a problem, and RELIS suggest further diagnostic steps to verify a DILI (e.g. temporary drug withdrawal, dose reduction).

The examples above follow the concept of PPPM [11, 30], where the RELIS services fit very well and demonstrate one of the viable ways for practical personalisation, preventive measures and, potentially, if the service is extended, also particular personal predictions for the patient at the particular stage of the disease.

Conclusion and expert recommendations

The official definition of personalised medicine is given in the European Council Conclusion on personalised medicine for patients (2015/C 421/03). According to this definition, the “personalised medicine refers to a medical model using characterization of individuals’ phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention” [25]. The PPPM not only is very well in agreement with this definition, but it substantially also extends it [11]. The RELIS service, in this context, can serve as a very practical example of person-centred and personalised attitude over the years and provides the basis for further improvements in healthcare. Questions to RELIS are motivated by the fact that clinical guidelines and other drug information sources often concern single diseases, the related symptoms and recommended drugs. These sources do not always provide adequate solutions to clinical problems. Thus, RELIS can “translate” clinical guidelines through a multi-professional collaboration into the real world of patients with polypharmacy, comorbidity and complex and sometimes contradictory laboratory results.

So far, this RELIS type of decision support in further development of PPPM is not getting attention in the healthcare service and science, perhaps because RELIS and similar DICs help individual, busy health professionals and not the opinion leaders. To reach a larger audience, and to advance medical services, RELIS has a strategy to contribute with experience in practical person-centred and personalised medicine to promote attitudes associated with PPPM in Norwegian healthcare.

A crucial element is our collaborating national network with one DIC in the regional university hospital in each of the four health authorities in Norway. Thus, the DIC is integrated and has credibility in the local healthcare service, both primary and secondary, and has responsibility for a specific geographical area. Another strategic choice in RELIS is collaboration between the regional DICs to provide additional drug information activities towards clinicians and patients.

Each RELIS centre is responsible for pharmacovigilance such as processing adverse drug reaction reports (ADRs) with a professional response to clinicians in their respective regions.

RELIS also share an academic detailing program to GPs and a successful patient service for pregnant and breastfeeding (Safe Mommy Medicine). The Safe Mommy Medicine database, with nearly 24,000 answers, can only be accessed by the staff but common patient experiences can be identified. The additional activities and a publication strategy through the homepage (www.relis.no) have been described previously [4].

Topics based on the experience of health professionals, or patients, are addressed in brief reviews and newsletters available on the homepage or in seminars for physicians or pharmacists in the respective regions. Cooperation with our grant administrator (the Norwegian Medical Agency) through an annual plan and meetings provides RELIS with the possibility to discuss prescribing problems of national interest and receive funding from the Norwegian Ministry of Health and Care Services to specific projects concerning rational use of drugs (e.g. national academic detailing programs). Thus, the core element in the RELIS strategy, and perhaps what separates us from national providers of drug information, is a “bottom-up” approach where the experience of the patients and health professionals are the starting point for all drug information activities. This is of particular relevance with regard to TCAM where the healthcare service and the public lack competence and the experience. RELIS receives numerous inquiries concerning interactions between TCAM and drugs, laboratory values and diseases. According to our experience of the last two decades, there is an increasing need for documentation and qualified academic opinion in this field of medicine [29]. RELIS vision is that our experience with practical personalisation and application of the attitudes promoted in PPPM could help to meet these challenges.

Compliance with ethical standards

Conflict of interest The author declares that he has no competing interests.

Ethical approval Not applicable.

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