Measuring effectiveness of risk minimisation measures in Estonia using health care databases

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Risk minimisation measures (RMMs) are intended to support the safe and effective use of medicines. Focusing on specific safety concern related to use of the medicine, additional RMMs outline what physicians and other health care professionals need to consider before prescribing a medicine, what specific monitoring should be done before and during treatment.

To evaluate whether RMMs serve their purpose, the knowledge on how the drug is used in clinical practice is necessary. Health care databases provide good opportunity for that – they contain data on large number of patients over many years, data are readily available and can be analysed rather quickly. Increasing variety of data available enhances the possibility to perform more in-depth studies.

As clinical behaviours, medicines available and patient populations differ between countries, the evaluation at national level is essential. In Estonia thanks to different e-solutions within the health care system (e-Health) there is an outstanding amount of electronic health care data. Unfortunately, a lot of it is also in free text format and is not usable for routine inquires.

Currently we can retrieve data from databases maintained by the Estonian Health Insurance Fund (EHIF). EHIF is responsible for purchasing health services and reimbursing prescription medicines on behalf of the insured population (covering approx. 95% of total population). Being a single public purchaser of care and covering almost the entire population makes EHIF data representative for the whole of Estonian population.

In Estonia out-patient prescriptions are issued and dispensed digitally since 2010 through the nation-wide system named Prescription Centre. For every prescription issued the date of issue, prescription number and type, patient's identification code, age, gender and diagnosis code, medicine's active substance, strength, dosage form and instructions for administration, rate of reimbursement and the doctor's name and speciality are saved in the database.

If a prescription is dispensed the date, package details and number of packages dispensed, amount paid by EHIF, the patient and in total, the name of the pharmacist and pharmacy and comments by the pharmacist (if there are any) are added to the database. Prescriptions can be distinguished by status – whether it is issued, dispensed or cancelled (incl. expired). Prescription Centre does not contain data about medicines used in hospital and over-the-counter medicines. So all the medicines used by a patient are not known.

Another EHIF database is Health Insurance Information System, which contains claims data of provided services of both – in- and outpatients. All invoices are submitted to EHIF electronically since 2004. Provided services are coded according to the approved services list. For provided healthcare services (e.g., examinations, procedures, medical devices) patient's

identification code, age, gender and diagnosis code, service code, date of service performed and speciality of physician can be identified.

A limitation possibly leading to little overestimation is that in EHIF health services list for some laboratory analysis several markers are coded as one health service, for example for immune screening different pathogens and hormones are coded in one service.

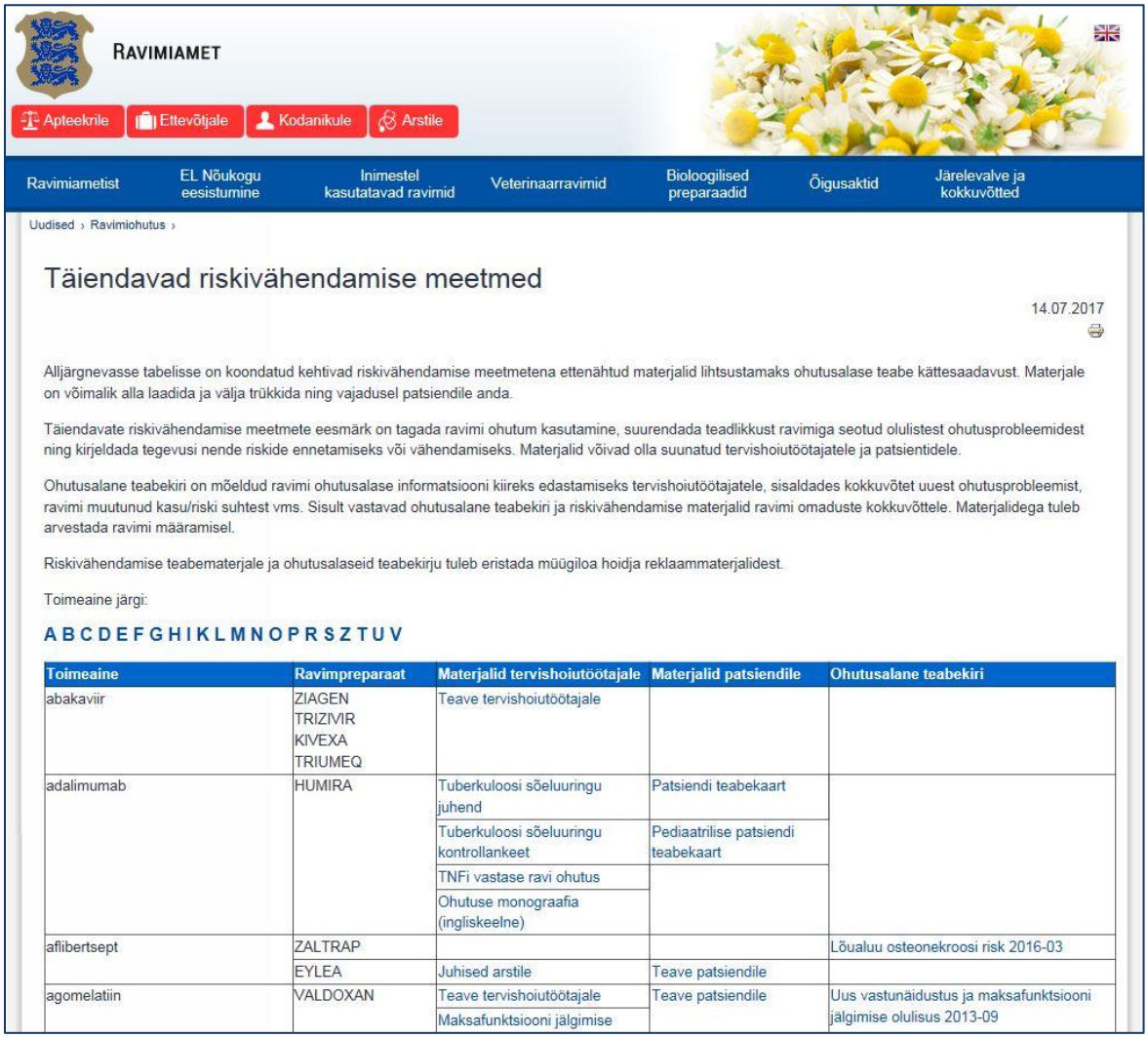
For data inquires EHIF removes the personal details of subjects and the ethical approval is not required. Pseudo-identification code is being used, which allows person-based linkage of medicine exposure and health services data.

Using EHIF data we can study the appropriateness of prescribing, like off-label use, contraindications, concomitant use and interactions, procedures and analysis performed in relation to the treatment when integrating drug use and health data.

Of course there are limitations which have to be considered. Buying a medicine does not necessarily mean that patient has used the medicine or that the medicine has been used as recommended, therefore actual exposure can differ from that calculated from dispensing data. Also diagnosis codes may not reflect real indications and patient's actual condition. Limitation of claims data is the lack of clinical detail of the patient – patient demographics, complaints and symptoms, response to treatment etc. Claims data refers that the procedure is done but doesn't provide information about the results and, for example whether laboratory analysis results were abnormal and therefore treatment should have been adjusted is not known. Also diagnoses and procedures may be inaccurately or incompletely coded and thereby influence the validity. To not exclude relevant information, the definitions must be carefully considered taking into account actual practice.

Nonetheless healthcare data offers valuable information on daily prescribing practice, also trends and progress over time can be identified. Studies conducted so far have shown that measures put in place are often poorly followed. With communication of the study findings we can highlight the deficiencies and remind the risks related to medicines. To improve availability and usage of latest version of aRMMs we have uploaded the materials to our website (Figure 1). By raising awareness of appropriate use of medicines the prescribing behaviours can be improved to support safer use of medicines.

Figure 1. Risk minimisation measures on State Agency of Medicines' website (www.ravimiamet.ee > ravimiohutus > täiendavad riskivähendamise meetmed).



RAVIMIAMET

Apteekrile | Ettevõtjale | Kodanikule | Arstile

Ravimiametist | EL Nõukogu eesistumine | Inimestel kasutatavad ravimid | Veterinaarravimid | Bioloogilised preparaadid | Õigusaktid | Järelevalve ja kokkuvõtted

Uudised › Ravimiohutus ›

Täiendavad riskivähendamise meetmed

14.07.2017

Alljärgnevasse tabelisse on koondatud kehtivad riskivähendamise meetmetena ettenähtud materjalid lihtsustamaks ohutusalase teabe kättesaadavust. Materjale on võimalik alla laadida ja välja trükkida ning vajadusel patsiendile anda.

Täiendavate riskivähendamise meetmete eesmärk on tagada ravimi ohutum kasutamine, suurendada teadlikkust ravimiga seotud olulistest ohutusprobleemidest ning kirjeldada tegevusi nende riskide ennetamiseks või vähendamiseks. Materjalid võivad olla suunatud tervishoiutöötajatele ja patsientidele.

Ohutusalane teabekiri on mõeldud ravimi ohutusalase informatsiooni kiireks edastamiseks tervishoiutöötajatele, sisaldades kokkuvõtet uuest ohutusprobleemist, ravimi muutunud kasu/riski suhtest vms. Sisult vastavad ohutusalane teabekiri ja riskivähendamise materjalid ravimi omaduste kokkuvõttele. Materjalidega tuleb arvestada ravimi määramisel.

Riskivähendamise teabematerjale ja ohutusalaseid teabekirju tuleb eristada müügiloa hoidja reklaammaterjalidest.

Toimeaine järgi:

A B C D E F G H I K L M N O P R S Z T U V

Toimeaine	Ravimpreparaat	Materjalid tervishoiutöötajale	Materjalid patsiendile	Ohutusalane teabekiri
abakaviir	ZIAGEN TRIZIVIR KIVEXA TRIUMEQ	Teave tervishoiutöötajale		
adalimumab	HUMIRA	Tuberkuloosi sõeluuringu juhend	Patsiendi teabekaart	
		Tuberkuloosi sõeluuringu kontrollankeet	Pediaatrilise patsiendi teabekaart	
		TNFi vastase ravi ohutus		
		Ohutuse monograafia (ingliskeelne)		
aflibertsept	ZALTRAP			Lõualuu osteonekroosi risk 2016-03
	EYLEA	Juhised arstile	Teave patsiendile	
agomelatiin	VALDOXAN	Teave tervishoiutöötajale	Teave patsiendile	Uus vastunäidustus ja maksafunktsiooni jälgimise olulisus 2013-09
		Maksafunktsiooni jälgimise		

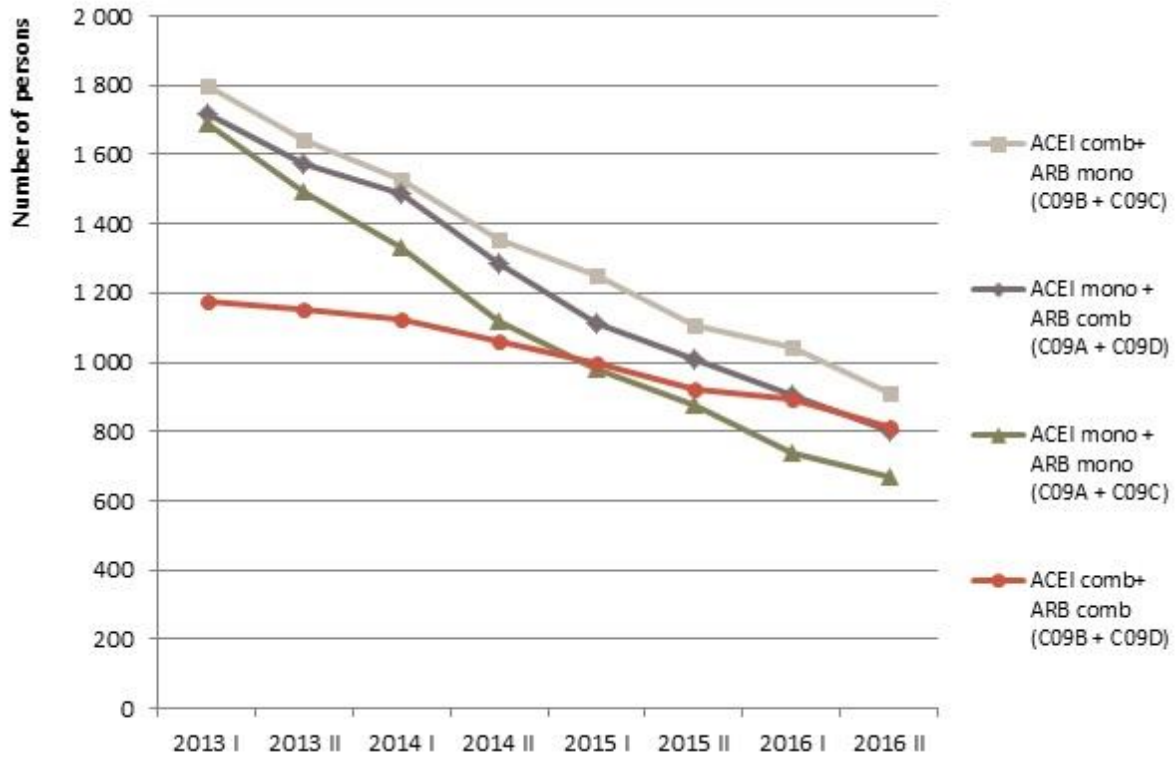
Some examples of the studies carried out are as follows:

Co-prescribing of renin-angiotensin system (RAS) acting agents is decreasing in Estonia

In light of the EMA's restriction of combined use of medicines affecting the renin-angiotensin system, we evaluated concomitant use of angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) in the period of 2013-2016. We retrieved data on patients who had purchased at least two prescriptions (presumably a four month treatment course) of both – ACEI and ARB or their combinations with diuretics during a half-year period. Within 4 years patients who received ACEI and ARB concomitantly decreased 50% and there were slightly over 3000 patients in the second half of 2016 (Figure 2). The total number of RAS users is around 250 000 in Estonia.

The decreasing trend of patients co-prescribed is a positive indicator of successful communication and implementation of the restriction.

Figure 2. Number of persons who used ACEI and ARB concomitantly.

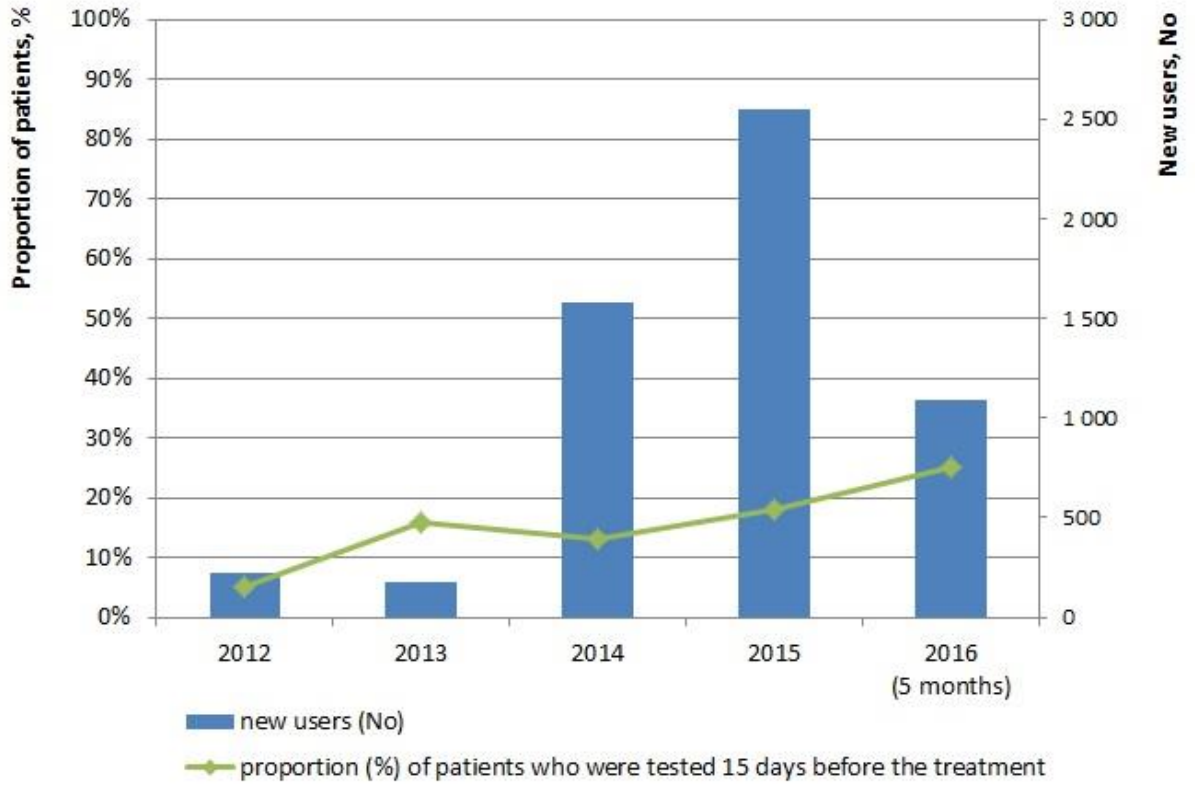


Adherence to Risk Minimisation Measures in prescribing agomelatine

After reports of liver injury in patients treated with agomelatine, the physician guide including a monitoring scheme and patient booklet as an additional RMM were implemented to avoid hepatotoxic reactions. We studied agomelatine incident users and how often liver function tests were performed prior and during treatment with agomelatine in the period from 2012 to first half of year of 2016. For liver function test we had to use laboratory analysis of enzymes which contains other markers besides liver enzymes.

During the study period slightly more than 5500 persons started treatment with agomelatine. 7% of patients were in age for what agomelatine is not indicated. Agomelatine was most commonly prescribed for depressive and anxiety disorders by psychiatrists. Surprisingly, majority of patients used agomelatine short-term, with a median duration of treatment of 2 months. On average, only in 17% of patients the test was performed prior to the treatment. Over the years it has slightly increased, but is still quite low (Figure 3). In total, in 44% of the patients at least one test was performed before the initiation of or during the whole treatment course.

Figure 3. Proportion of patients who the liver enzyme test was performed prior to the initiation of treatment with agomelatine.



Poor adherence to the liver monitoring scheme indicates the need for continuing education and communication of aRMMs.

Prescribing valproic acid for women of childbearing age

In relation to the EMA's new review of valproic acid use in pregnancy and women of childbearing age, we undertook a study to describe the prescribing practice of valproic acid for women of childbearing age in Estonia.

We studied valproic acid new users in period of 2015-2016. Alternative treatment was considered if any of medicine for epilepsy and bipolar disorder were purchased at least once during year prior valproic acid. Prescriptions of hormonal contraceptives and invoices of non-hormonal intrauterine devices we defined as effective contraception. For pregnancies we used invoices data of confirmed pregnancies and abortive outcomes.

Of all new valproic acid users 20% were women of childbearing age (15-49 years). Contrary to our expectations valproic acid was more often prescribed for mental and behavioural disorders (57%) than for epilepsy (30%). In 45% valproic acid was prescribed for registered indications – epilepsy and bipolar disorder. Alternative treatment was more used in bipolar disorder than epilepsy, which is understandable as for bipolar the choice of medicines is wider. Use of effective contraception was very low, particularly in patients with other mental and behavioural disorders. In total, effective contraception was used at the same level as estimated in total population. During valproic acid treatment we identified three pregnancies; of those two were terminated by medical abortion. One pregnancy continued and the valproic acid was discontinued after pregnancy was diagnosed. Detailed information are in the Table 1.

Table 1. Characteristics of women of childbearing age initiating valproic acid treatment by indication.

Indication (ICD-10 code) Characteristic	epilepsy (G40, G41)	bipolar disorder (F31, F30)	other mental and behavioural disorders (F00–F99)	migraine (G43, G44)	other
Number of WCB (total 299) treatment initiated 2015 treatment initiated 2016	91 (30%) 47 44	46 (15%) 19 27	124 (41%) 56 68	32 (11%) 12 20	6 (2%) 3 3
Median duration of treatment episode (days)	83	90	40	20	61
Alternative treatment during one year prior valproic acid	38 (42%)	31 (67%)	-	-	-
Effective contraception at the initiation of valproic acid during whole valproic acid treatment	12 (13%) 9 (10%)	9 (20%) 9 (20%)	11 (9%) 8 (6%)	8 (25%) 8 (25%)	1 (17%) 1 (17%)
Number of pregnancies during study period during valproic acid treatment	6	3	15 3	5	

Study results show that aRMMs and product information are not accurately followed by the physicians and further amendment of the aRMM and communication is essential.