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The development and validation of coded scripts to assess drug related problems due to anticholinergic burden and medication complexity in large study databases

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Abstract

The drug burden index (DBI) and medication regimen complexity index (MRCI) are validated tools which identify patients who may experience drug related problems (DRPs) due to anticholinerg and/or sedative burden and medication complexity, respectively. We set out to create two coded scripts in order to identify these patients in large study databases.

We translated the established algorithms for DBI and MRCI into an R script. The scripts were developed in a large trial database of elderly patients with polypharmacy, and subsequently the performance was validated in this database. DBI and MRCI scores for these patients were calculated by our scripts, and the resulting scores were thereafter compared to manual calculations in stratified samples. Validation was expressed as the proportion of identical score pairs. We assessed four scenarios for imputing the daily frequency of as needed medication for the DBI coded script. Additionally, the MRCI coded script was validated by comparing the ranking of six varying test regimens according to the coded script with the ranking according to the original published MRCI tool.

Both DBI and MRCI coded scripts showed a high proportion of identical score pairs (91.5% and 88.1% for two scenarios of the DBI calculation, and 94% for the MRCI coding). The mean difference between all selected score pairs were minimal. Excluding as needed medication from the DBI computations, led to underestimation of the total anticholinergic burden. Our MRCI coded script showed an identical ranking of the six test regimens.

In conclusion, we have achieved two validated coded scripts to calculate the DBI and the MRCI in large study databases, allowing us to identify patients who may experience DRPs due to anticholinerg burden and medication complexity in large study databases. The actual use of as needed medication is usually not recorded. We propose to impute as needed medication with a median value to avoid underestimation of the DBI score.

Introduction

Elderly people suffering from multimorbidity often use multiple medications (polypharmacy). Although individual medications relieve causes or symptoms of specific diseases which they are intended for, the combination of multiple medications may give rise to unintended drug related problems (DRPs).[1,2] DRPs are defined as “events or circumstances involving drug therapy that actually or potentially interfere with desired health outcomes”.[2]

To study the intricacies of the association of DRPs with unfavorable health outcomes, such as loss of quality of life, large study databases with elderly people can be an important research platform. In order to use these databases for this purpose, patients with DRPs will have to be identified and drug related burden will have to be quantified.

The drug burden index (DBI) and the medication regimen complexity index (MRCI) are validated tools to identify patients who may experience DRPs.[3,4] The DBI measures a patient's total exposure to medications which have clinically significant anticholinergic and/or sedative properties.[3,5] These medications may lead to poorer physical and cognitive function due to adverse drug events (e.g. blurred vision, confusion, sedation). Higher DBI scores are associated with falls, frailty, hospitalization, and mortality.[6] The MRCI quantitatively expresses the medication complexity due to different dosage forms, multiple dosage frequencies and special instructions per individual drug.[7] Higher MRCI scores may lead to a diminished adherence, which is linked to adverse drug events and to unplanned hospital admissions.[8] Although these tools are widely used in medical practice and research, details on exact implementation and subsequent validation in large study databases are usually not well described.

In previous research, the DBI has been automated and validated.[9] However, this DBI calculator was made for the purpose of a Clinical Decision Support Systems (CDSS) in practice. Furthermore, this DBI calculator has limited accessibility.[9] The MRCI has been coded specifically suited for an Electronic Health Record database. The information regarding the "special instructions" (e.g. relation to food) was included based on information given in the free text ‘comment’ fields, which in study databases is not always available. Therefore, this code has limited usability in large study databases. In summary, although these tools were automated and validated to identify patients with potential DRPs in a clinical setting, they are neither (freely) available nor intended to be used in large study databases. It is therefore necessary to develop and validate coded scripts for these tools in order to obtain robust methods to identify patients with potential DRP in large study databases.

The aim of this study is to develop and validate two newly coded scripts for established tools (DBI and MRCI) to detect patients who may experience DRPs in large study databases.

Methods

Study design

This study was performed using cross-sectional data from the Optimizing Therapy to Prevent Avoidable Hospital Admissions in Multimorbid Older Adults (OPERAM) study. OPERAM is a multicenter cluster randomized controlled trial which studied the effect of a structured pharmacotherapy optimization intervention on drug related hospital admissions compared to usual care in elderly patients with multimorbidity and polypharmacy.[10]

Study population

In the OPERAM study, 2008 hospitalized elderly adults (aged 70 or over) with multimorbidity and polypharmacy were included. Multimorbidity was defined as three or more chronic conditions and polypharmacy as the daily use of five or more drugs. All participants had been admitted to one of the four participating hospitals located in four European countries: Switzerland, The Netherlands, Belgium and the Republic of Ireland. Patients were only included when their expected length of stay was long enough for the intervention to be applied. Patients were excluded if transfer to palliative care was imminent, if they had a recent medication review before hospitalization, or if no written informed consent could be obtained.[10]

We used data of 2005 participants from the OPERAM study for whom medication information was available at the first day of inclusion in the trial. We considered the first day of inclusion in the trial as our reference date (baseline). All medications in the OPERAM study have been coded according to the globally used medication classification anatomical therapeutic chemical (ATC) codes.[11] Medication data are available on dosage route, dosage frequency and drug strength.

The Drug Burden Index

Background

The DBI calculates per patient the anticholinergic and sedative burden by showing the cumulative exposure of anticholinergic and/or sedative medications.

The DBI is an equation following $DBI = \Sigma\ D / (\delta + D)$, where D is the daily dose taken for a specific anticholinergic and/or sedative drug, and δ is the minimum effective daily dose for that drug.[3] Each drug has a burden score between 0 and 1. A score of 0.5 indicates that an individual is exposed to the minimum effective daily dose. The total DBI is the sum of the burden scores of all the anticholinergic and/or sedative medications.[5] An example of a DBI calculation can be found in Supplemental Table A.

Development of the coded script

The set of medications with anticholinergic and/or sedative effects and their minimum effective daily dose (δ) per route of administration which we used in the coded script were based on the validated Master Drug Burden List, constructed by Byrne et al.[11] The δ was noted in the unit milligram per day. When the δ in the Master Drug Burden List was missing for a particular route of administration, it was added with the minimum recommended daily dose as listed by the KNMP Kennisbank.[12] The minimum recommended daily dose could be used as an estimate of the minimum effective daily dose. [5]

The DBI medications in the database were identified using ATC codes. When the daily dose could not be determined (e.g. 'unit' as unit) or was missing, the median dose for the study population was used in the calculation instead. This is in line with earlier studies.[13] Two pharmacists evaluated possible coding errors (e.g. an typo in the strength of a medication which is not on the market, e.g. 500 mg when the product on the market contains 50 mg).

The Medication Regimen Complexity Index

Background

The MRCI was developed to quantitatively express medication complexity. The MRCI consists out of three different components: the dosage forms (A), dosage frequencies (B), and additional instructions (C). Each component has its own scoring scheme, featuring a weight for the patient's burden.[7]

Component A consists of a list of different dosage routes and their forms. For each form a different weighting score from 1 to 5 is applied. Each dosage form is scored only once, regardless of the total number of occurrences of that dosage form. Component B is a list of dosage frequencies. For each frequency the number of medications is summed and subsequently multiplied by their weighting. Component C is a collection of additional instructions for use, specific for each medication. Similarly to component B, for each instruction the number of medications is summed and subsequently multiplied by their weighting. By summing the sub scores for the three components, the total MRCI is determined. The total MRCI score has no upper limit.[7] An example of a MRCI calculation can be found in Supplemental Table B.

Development of the coded script

Dosage forms (needed for component A) were not included in the database. The Dutch drug database "G-standaard" and the "NHG Standaard" inhalation guidelines were used to ascertain whether certain ATC codes could be linked to unique dosage forms within a given route of administration according to the MRCI tool.[14–16] These results can be found in Supplemental Table C. When an ATC code was available in multiple dosage forms, the dosage route and the dosage unit in the database were used to estimate the dosage form of the drug. In these cases, the most common dosage form within a dosage route was chosen to serve as the assumed dosage form (stated in Supplemental Table D). When the dosage route in the database was coded under "other", the ATC-level was used to determine the assumed dosage form (Supplemental Table E).[17]

For component B, the dosage frequencies as noted in the database were matched against the official MRCI table B. When the dosage frequency in the database was missing, the median frequency for the study population was used in the calculation.

Additional instructions for use (needed for component C) were not included in the data collection for the OPERAM study. We used label texts available in the G-standaard to determine whether certain additional instructions for use could be linked to ATC codes, regardless of the dosage form or the brand used. We focused on the oral route of administration only since component C is most applicable to oral dosage forms.

In the OPERAM study a total of 1123 distinct ATC codes were involved. All label texts which occurred by these ATC codes in the G-standaard were extracted into spreadsheets. A researcher made a selection of label texts which could contribute to the additional instructions for use according to the MRCI component C. Two pharmacists reviewed the spreadsheets and adjusted when necessary. The final version of the relevant label texts linked to an additional instruction for use can be found in

Supplemental Table F. We linked an additional instruction for use to an ATC code when one or more of the corresponding relevant label texts occurred with each oral dosage form, regardless of the brand.

The additional instructions “break or crush tablet" and “dissolve tablet/powder” were also linked to an ATC code when component A revealed that the ATC code had respectively breakable or dissolvable oral dosage forms only.

The final version of the additional instructions for use linked to unique ATC codes in combination with the oral dosage route which we used in our code can be found in Supplemental Table G. The additional instructions for use which could not be derived for the participants in the OPERAM study or unique ATC codes are: “multiple units at one time (e.g. 2 tabs, 2 puffs)”, “variable dose (e.g. 1-2 caps, 2-3 puffs)”, “tapering/increasing dose” and “alternating dose (e.g. one mane & two nocte)”.

Validation phase

The newly created coded scripts of the two tools were checked by a pharmacist. Subsequently, we determined the DBI and the MRCI for all 2005 participants with the coded scripts. For the validation phase, we took samples of tertile subgroups of the final score.

For the validation of the DBI script, we randomly selected 20 participants from the group with a DBI score of 0. Subsequently, we took 39 participants with a DBI higher than zero. We sampled 10 participants out of each tertile subgroup from the group with a positive DBI score. Additionally, we took another sample of 9 participants out of the subgroup with a total DBI score greater than 3.0, because outliers were expected to have the highest risk of an invalid DBI score.

For the validation of the MRCI script, we took a sample of 10 participants out of the lowest tertile subgroup, and a sample of 20 participants from both the middle and upper tertile subgroup. The MRCI score does not include zero, so an extra group was not added to the three tertile samples.

The DBI and MRCI of the selected participants were manually calculated by a researcher for each selected participant. The upper tertile subgroup was validated together with the pharmacist. These scores were designated as the golden standard.

For a secondary validation of our MRCI coded script, we used the validation method which the developers of the original MRCI checklist (George et al.) used to validate their tool.[4] George et al. tested the original MRCI checklist by determining the MRCI score for 134 different medication regimens taken from patients with moderate to severe chronic obstructive pulmonary disease (COPD). A selection of six test regimens (Supplemental Table H) with a spread of MRCI scores was submitted to a 5-member expert panel. The panel members ranked these six test regimens on medication complexity using their professional judgment and they reached a consensus ranking. This consensus ranking corresponded to the ranking according to the absolute values resulted from the MRCI tool. Based on this result, George et al. considered their tool valid.[4]

We translated the set of six test regimens from George et al. into the respective equivalents in the OPERAM database format (Supplemental Table H) and determined the MRCI scores using our coded script. To check whether the concept of medication complexity according to the original tool was well represented in our script, we compared the ranking of George’s expert panel with the ranking by our coded script.

Analysis

Agreement

The results of the manual calculations were compared to the results from the newly coded scripts. Agreement between the newly created coded scripts and the manual calculations was assessed by calculating the proportion of scripted scores which were identical to the manual scores (%). Furthermore, we assessed the mean difference between the pairs of scores (95% CI).

Sensitivity analysis

In most cross sectional database studies, as needed medications were excluded for the DBI calculation.[6] To assess which frequency of as needed medication gave the most representable results for the total DBI score, we calculated the DBI with four different frequencies for the anticholinergic and/or sedative medications that were prescribed on an as needed basis. This was done for all 2005 participants in the database. In one scenario we excluded the as needed medication (scenario A). In the other three scenarios, we considered the daily frequency of as needed DBI medication as once a day (scenario B), the maximum prescribed frequency a day (scenario C), and the median dose a day (scenario D), respectively.

To determine the impact of the exclusion of as needed medication on the final DBI score, we plotted the DBI scores from scenario A against the DBI scores from the other three scenarios. We also compared the mean differences in the DBI score from the four scenarios by a Kruskal-Wallis test and subsequently a post-hoc analysis using the Dunn test. A p-value < 0.05 was considered statistically significant.

Ranking agreement (MRCI)

Spearman's rank-order correlation coefficient (Rho) was used for comparing the ranking of the six test regimens according to George et al. with the ranking by the newly created coded MRCI script where a value of 1 indicates a perfect positive relationship between the two rankings. A p-value < 0.05 was considered statistically significant.

Outcome

The primary outcome of this study is the agreement between the newly coded scripts for the DBI and MRCI and the manual calculation (golden standard) of these tools, as expressed by the proportion of identically calculated scores.

The secondary outcome of this study is the impact of the inclusion of the as needed medication on the final DBI score in comparison with the total DBI score in cases when as needed DBI medication is excluded.

Software program

The development of the coded scripts and the statistical analyses were done using the R statistical package (version 4.1.2).

Results

Study Population

The baseline characteristics of our study population are presented in Table 1.

Table 1 Characteristics of study population of the OPERAM study at baseline

Characteristics*	
Age (years) (median, IQR)	79.00 (74.00; 84.00)
80 and older (n, %)	923 (46.2%)
Female (n, %)	892 (44.6%)
Body mass index (kg/m2) (median, IQR)	26.21 (23.44; 29.74)
Current smoker (n, %)	157 (7.9%)
No of comorbidities (median, IQR)	11.00 (8.00; 16.00)
No of drugs (median, IQR)	9.00 (6.00; 12.00)
Hyperpolypharmacy (10+ medications) (n, %)	841 (42.2%)

**Table based on 1998 participants, patients without data on quality of life were excluded.*

The Drug Burden Index

The total DBI score

All analyses were performed in four scenarios: exclusion of as needed medication (scenario A), as needed medication with a daily frequency of once a day (scenario B), as needed medication with the maximum prescribed frequency a day (scenario C), and as needed medication with the median dose a day (scenario D).

At baseline, a total number of 21,113 instances of medications were involved. From these 21,113 instances, 2,367 medications were identified as anticholinergic and/or sedative according to the Master Drug Burden List.[11] These DBI medications were taken by 1164 participants in the OPERAM study at baseline. 399 DBI medications were prescribed on an as needed basis (i.e. 16.9 % of the total number of DBI medication). When as needed medication were excluded from the total DBI calculation (scenario A), the number of participants in the OPERAM study with a positive DBI score at baseline decreased to 1061, as 103 participants only used DBI medication on as needed basis.

The total DBI score for all 2005 participants follows a right-skewed distribution in all four different scenario's (figure 1). In scenario A, the total DBI score of the 2005 participants had a range of 0.0000 and 4.2881, with a median of 0.3333 (IQR = 0.0000 – 0.8333). Including the as needed medication in the DBI calculation, the total DBI score range extends to a maximum of 5.2000 (scenario B), 6.0889 (scenario C) and 5.6952 (scenario D). The median in scenarios B, C, and D were in all cases 0.50000. The differences between scenario A and the other scenarios were all statistically significant ($P < 0.05$). The differences in mean among scenario B, scenario C and scenario D were not statistically significant (P-value > 0.05).

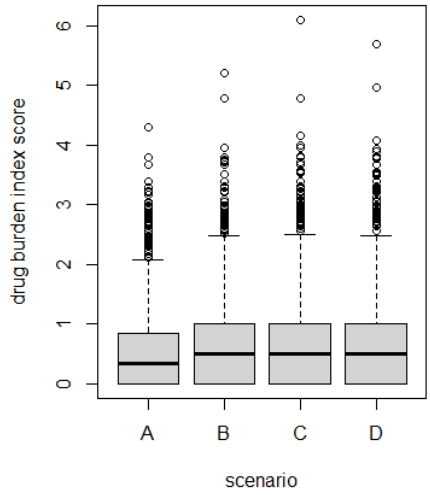

Figure 1 The distribitution of the total DBI score for all 2005 participants at baseline

The DBI scores for all 2005 participants from scenario A were plotted against the DBI scores from the other three scenarios (figure 2). Figure 2 shows the deviation of the DBI score between scenario A and scenario B to D when as needed medication were included. The level of deviation of scenario A is similar for all three other scenarios.

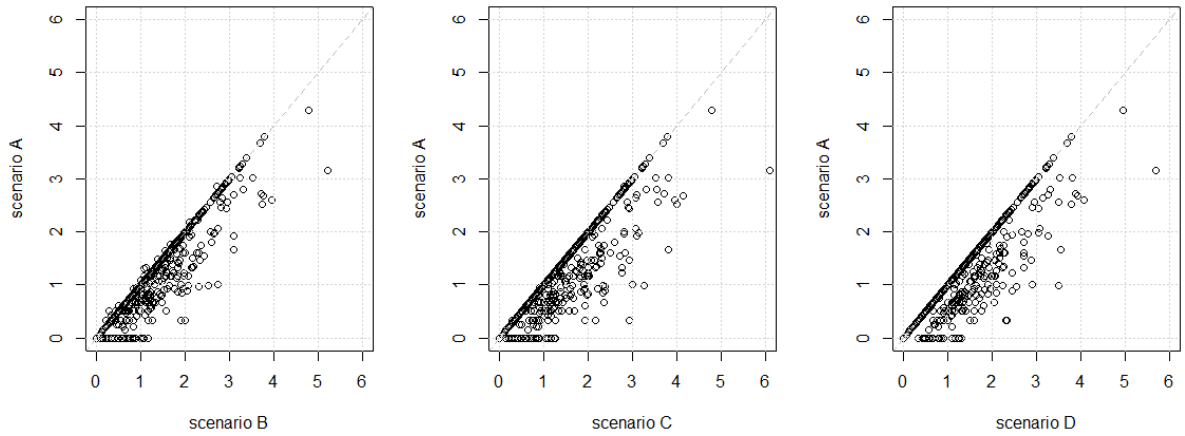

Figure 2 The differences of the total DBI score for all 2005 participants at baseline compared to exclusion of as needed medication (scenario A) where scenario B: as needed frequency as once a day, scenario C: as needed frequency as the maximum prescribed frequency a day, scenario D: as needed frequency as median dose

Validation phase

We validated scenarios with some imputation for as needed medication, because these scenarios take into account the as needed medication for the full number of participants (scenario B, C, and D). Validation of scenario D however was not feasible, because cohort-wide median values would have to be available which is not the case when manually computing the DBI score for individual participants. We therefore present the results scenario B and C.

The manually calculated scores of the selected participants were compared with the total DBI score for those participants calculated according to the coded script. The DBI score per participant for both the manual and coded script approaches are in Supplemental Table **I**. The proportion of identical DBI scores was 91.5% for scenario B, with a mean difference between all coded pairs of 0.01 (95% CI -0.08 – 0.12) (Table 2). The mean difference for the disconcordant pairs only was 0.16 (95% CI -0.03 – 0.36). For scenario C the proportion of identical DBI scores was 88.1% (Table 3). The mean difference between all coded pairs was 0.01 (95% CI -0.09 – 0.11). The mean difference for the disconcordant pairs only was 0.08 (95% CI -0.20 – 0.36).

The proportion in both scenarios was not 100%, because some regimens had missing information on the medication dosage (e.g. medication strength). The median dosage which was imputed by the coded script did not match the imputed dosage which the pharmacist used based on most likely indication and pharmaceutical guidelines.

Table 2 Validation outcomes for the DBI score in scenario B

	Manual approach (n)	**Corresponding DBI score using coded script (n)**	**Proportion identical DBI scores (%)**
Total DBI score = 0	20	20	100 %
Total DBI score > 0 & < 0.6666667	10	8	80 %
Total DBI score > 0.6666667 & < 1.20558824	10	10	100 %
Total DBI score > 1.20558824 & < 5.0529617	10	8	80 %
Total DBI score > 3	9	8	88.89 %
Total	59	54	91.5 %

Table 3 Validation outcomes for the DBI score in scenario C

	Manual approach (n)	Corresponding DBI score using coded script (n)	Proportion identical DBI scores (%)
Total DBI score = 0	20	20	100 %
Total DBI score > 0 & < 0.6666667	10	7	70 %
Total DBI score > 0.6666667 & < 1.20558824	10	9	90 %
Total DBI score > 1.20558824 & < 5.0529617	10	8	80 %
Total DBI score > 3	9	8	88.89 %
Total	59	52	88.1 %

The Medication Regimen Complexity Index

Validation phase

The overall MRCI score for 2005 participants of the OPERAM study at baseline ran between 2.00 and 88.50 with a median score of 19.50 (IQR = 13.50 – 27.50).

The manually calculated scores were compared with the total MRCI score calculated according to the coded script. The results of the MRCI per participant for both the manual and coded script approaches are in Supplemental Table J. Overall the total proportion which was identically calculated for both approaches was 94 % (Table 4). The mean difference between all coded pairs was 0.05 (95% CI -0.67 – 0.77). In three instances, the calculations of the coded script did not match the manual calculation. The mean difference for these disconcordant pairs only was 0.83 (95% CI -2.16 – 3.83). In all these three instances, the regimens had missing information on the medication frequency (component B). The median frequency which was imputed by the coded script did not match the imputed frequency which the pharmacist used based on most likely indication and pharmaceutical guidelines.

Table 4: Validation outcomes for the MRCI coded script

	Manual approach (n)	Corresponding MRCI score using coded script (n)	Proportion identical MRCI scores (%)
Total MRCI score < 15.0	10	9	90 %
Total MRCI score > 15.0 & < 23.5	20	19	95 %
Total MRCI score > 23.5	20	19	95 %
Total	50	47	94 %

Ranking agreement (MRCI)

The ranking of George's validation set of six test regimens (Supplemental Table H) according to their 5-member expert panel is given in table 5, alongside our manually recreated MRCI score from these regimens. The MRCI scores of these six regimens were also calculated using our coded script. These corresponding ranking and their absolute values are also given in table 5.

The MRCI scores vary widely between the MRCI tool itself and the created code. However, the ranking is similar. A significant correlation was observed between the two rankings (Spearman's Rho = 1.00 and P-value = 0.003).

Table 5: Correlation between rankings using the MRCI tool and using the coded script

Test regimens from George et al. (Supplemental Table H)[4]	**Ranking according to George et al.** [4]	**Manually recreated MRCI scores for George's validation regimens**	**Ranking according to coded script**	**MRCI score according to coded script**
A	1	7	1	5
B	2	16.5	2	11.5
C	3	24.5	3	14.5
D	4	30.5	4	34.5
E	5	42.5	5	38.5
F	6	72.5	6	68

Discussion

This study outlines the development and validation of two newly coded scripts for the DBI and the MRCI to detect patients who may experience DRPs in large study databases. We thereby showed that excluding as needed medication in the DBI calculation can lead to underestimation of the DBI score, and that imputing a median daily dose for as needed medication should take place.

In previous research, many studies on DBI calculation excluded as needed medication, when assessing the true frequency of a patient's use of as needed medication was not feasible.[18,19] However, this method may give an underestimation of the final DBI score.[6] Therefore, we calculated the total DBI score for four different scenarios, one scenario in which as needed medication was excluded, and three scenarios with different ways of assuming values for the frequency of as needed medication.

In our study excluding as needed medication led to a decrease in 16.9% DBI medication prescriptions. As a result, for 103 participants a DBI score unduly could not be calculated (i.e. 5% of the study population) and for 205 participants who used both chronic and as needed DBI medication, the final DBI score was diminished. Each of the three scenarios with imputed frequency data for as needed medication (scenario B, C, D) differed significantly from this scenario where as needed medication was excluded (scenario A). So, our results confirm that excluding as needed medication lead to biased estimates, therefore it is clinically relevant to include some estimate for as needed medication in the DBI calculation.

The other three scenarios where as needed medication was considered as daily use with three different frequencies per day, showed consistent results with no statistically significant differences. We recommend to insert the median daily dosage for as needed medication. As stated, the median daily dosage was also used in the calculation when the daily dosage for chronic DBI medication was missing, just like other studies did.[13] Applying the median daily dosage for as needed medication (scenario D, figure 1), gave intermediate results compared to the minimum and maximum dosage imputation (scenario B and C, respectively). Also, for reasons of consistency, we recommend to insert the median daily dosage for as needed medication, because we used median value imputation for missing values on chronic DBI medication as well.

We noticed that our scripted MRCI scores for the six test regimens from George et al. were lower than the manually recreated MRCI scores of those regimens (Supplemental Table H). This may be a result of the fact that the database we used to develop the coded script did not always provide sufficient detail on dosage forms, additional instructions for use, and dosage frequency. Dosage forms had to be derived from ATC codes and dosage route. When this was not possible, the dosage form was based on the most common form within a particular dosage route, whereas with a manual MRCI calculation of George's test regimens, these information could be directly extracted from the regimen. Therefore, the MRCI score of our coded script sometimes leads to an underestimation of the total weighting for component A, because not all assumed dosage forms based on the dosage route are sufficiently specific. Furthermore, the MRCI scores of our coded script may lead to an underestimation of the total weighting for component C, because four out of the ten additional instructions for use according to the MRCI, could not be recognized in the large study database. At the same time however, the six instructions which could be derived, may give some overestimation of the total weighting for component C, because the additional instructions linked to ATC codes was not always recorded in the original test regimens which George et al. used. For component B limitations applied because our trial data format only reported frequencies per day, week, month, year, but not frequencies per hour. Therefore, component B is prone to underestimation as well. So in conclusion, our script provides

conservative estimates for the actual MRCI score. False positive scores are therefore unlikely and true effects may be larger than reported by our script. Despite the differences of MRCI scores, the ranking was exactly similar (Spearman's Rho = 1.00 and P-value = 0.003). Therefore, we have confirmed that the concept of medication complexity according to the original tool was well represented in our script.

Our validated scripts could be used in future pharmaco-epidemiological research. Although our newly created variables for the OPERAM database can be used as determinants or covariates in new studies to be performed using the OPERAM data, the main asset of our project is that by harmonizing variable coding our script could be extended to large clinical trial databases where information on prescriptions is also limited.

Our scripts take into account missing variables for dosage forms and additional instructions for use by imputing values based on information derived from the G Standaard (Dutch drug database).[14] Therefore, we have created two lists of added information for ATC codes. One list consists out of ATC codes which have a unique dosage form within a given dosage route. The other list provides information on ATC codes which have an additional instruction for use for all oral dosage forms. These lists may aid other research projects where this particular information is needed.

A strong feature of our study is the large sample size of our database. The OPERAM database represents a hospitalized, elderly population with multimorbidity. The data of OPERAM was collected in a clinical trial setting, and therefore data quality is considered high.

However, we have to address several limitations. Despite the high quality of the OPERAM database, we had to deal with some missing data in the medication variables. These missing values were in the coded script imputed by inserting overall median value. In cases where a prescriptions only occurs twice, with one of them being missing, imputing would mean plain copying the other value, rather than applying some weighted aggregate. This way of inserting median values may have led to a bias. Also, the pharmacist did not have access to those median values when assessing medication records of individual participants during the validation phase. Therefore, the missing values were imputed based on most likely indication and pharmaceutical guidelines. Due to this different handling of missing information in the medication data, we did not reach a sensitivity of 100%.

Another limitation of our study involves the enriching of the OPERAM database with external data sources. The Master Drug Burden List by Byrne et al. was used to identify medications which may have anticholinergic and/or sedative properties. They based their definition of anticholinergic and/or sedative properties on information from several drug monographs. They considered a medication as anticholinergic when blocking the muscarinic receptors and based on (very) common side effects which refer to anticholinergic burden (e.g. blurred vision). Sedative properties were only based on (very) common side effects related to drowsiness. As Byrne et al. point out in their study, there is no golden standard definition describing anticholinergic and sedative medications.[11] This means that other anticholinergic burden tools may use different methods to identify medication which may cause anticholinergic and/or sedative burden. For example the medication used in the ACB calculator is based on information derived from a Medline literature search.[20] Because of this lack of a golden standard, we cannot be completely sure about the correct assignment of anticholinerg and/or sedative medications. Furthermore, this Master Drug Burden List was specifically created according to the prescribing practice in Ireland and has not been updated since 2018.[11] Our data was collected in Switzerland, The Netherlands, Belgium and the Republic of Ireland. [10] Adaptation of the list to settings in other countries could enhance precision.

For the MRCI computation we added extra information from the G Standaard. The final list where ATC codes are linked to additional instructional properties has been reviewed by a pharmacist. However,

the G standaard appeared to be not as complete as we hoped for. For example, drugs for insomnia (e.g. zolpidem, temazepam) did not have the label text "take before sleeping", so the additional instruction "take at a specific time" could not be linked, whereas in daily practice this information would be included in the oral communication when the medication is dispensed. Therefore, component C may give an underestimation of the actual additional instructions a patient has to deal with.

In future research, both coded scripts could be tightened by making more precise assumptions when enriching the database with external sources.

Also in future research, a third coded script which identifies patients who may use potentially inappropriate medication (PIM), including overuse, misuse, or underuse of medication, could be developed. By applying STOPP START criteria to a large study database, a more complete assessment of drug related burden could be obtained.[21,22]

In conclusion, we have achieved two validated coded scripts to calculate the DBI and the MRCI in large study databases, allowing us to identify patients in such data sets who may experience DRPs due to anticholinerg burden and medication complexity.

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Supplementary Table A

An example of a drug burden calculation using the DBI tool. This example is from Kouladjian et al. (2014).[6]

Table S1: Example of a drug burden index calculation

Medication	**Daily dose (D)**	**Minimum recommended dose (δ)**	**Individual DBI score**
Irbesartan 300 mg, daily	300 mg	75 mg (no DBI medication)	0
Darifenacin 15 mg, daily	15 mg	7.5 mg	0.67
Temazepam 7.5 mg, at night	7.5 mg	7.5 mg	0.50
Acetaminophen 300 mg, 2 tablets tds	1,800 mg	300 mg (no DBI medication)	0
Codeine 15 mg, 2 tablets tds	90 mg	120 mg	0.43
			1.60

DBI formula = $\sum D / (D + \delta)$ for each medication with anticholinergic or sedative effects.

Total DBI score = $0 + (15 / (15 + 7.5)) + (7.5 / (7.5 +7.5)) + 0 + (90 / (90 + 120)) = 1.60$

Supplementary Table B

An example of a medication complexity calculation using the MRCI tool. [4]

A) Circle the weighting corresponding to each dosage form (ONCE ONLY) present in the regimen.

Dosage Forms		Weighting
ORAL	Capsules/Tablets	1
	Gargles/Mouthwashes	2
	Gums/Lozenges	2
	Liquids	2
	Powders/Granules	2
	Sublingual sprays/tabs	2
TOPICAL	Creams/Gels/Ointments	2
	Dressings	3
	Paints/Solutions	2
	Pastes	3
	Patches	2
	Sprays	1
EAR, EYE & NOSE	Ear drops/creams/ointments	3
	Eye drops	3
	Eye gels/ointments	3
	Nasal drops/cream/ointment	3
	Nasal spray	2
INHALATION	Accuhalers	3
	Aerolizers	3
	Metered dose inhalers	4
	Nebuliser	5
	Oxygen/Concentrator	3
	Turbuhalers	3
	Other DPIs	3
OTHERS	Dialysate	5
	Enemas	2
	Injections: Prefilled	3
	Ampoules/Vials	4
	Pessaries	3
	Patient controlled analgesia	2
	Suppositories	2
	Vaginal creams	2
	Total for Section A	

B) For each medication in the regimen tick a box [√] corresponding to the dosing frequency. Then, add the no. of [√] in each category and multiply by the assigned weighting. In cases where there is no exact option, choose the best option.

Dosing Frequency	Medications	Total	Weighting	Weighting × No. of medications
Once daily			1	
Once daily prn			0.5	
Twice daily			2	
Twice daily prn			1	
Three times daily			3	
Three times daily prn			1.5	
Four times daily			4	
Four times daily prn			2	
q 12h			2.5	
q 12h prn			1.5	
q 8h			3.5	
q 8h prn			2	
q 6h			4.5	
q 6h prn			2.5	
q 4h			6.5	
q 4h prn			3.5	
q 2h			12.5	
q 2h prn			6.5	
prn/sos			0.5	
On alternate days or less frequently			2	
Oxygen prn			1	
Oxygen <15hrs			2	
Oxygen >15hrs			3	
	Total for Section B			

C) Tick a box [√] corresponding to the additional directions, if present in the regimen. Then, add the no. of [√] in each category and multiply by the assigned weighting.

Additional Directions	Medications	Total	Weighting	Weighting × No. of medications
Break or crush tablet			1	
Dissolve tablet/powder			1	
Multiple units at one time (e.g. 2 tabs, 2 puffs)			1	
Variable dose (e.g. 1-2 caps, 2-3 puffs)			1	
Take/use at specified time/s (e.g. mane, nocte, 8 AM)			1	
Relation to food (e.g. pc, ac, with food)			1	
Take with specific fluid			1	
Take/use as directed			2	
Tapering/increasing dose			2	
Alternating dose (e.g. one mane & two nocte, one/ two on alternate days)			2	
	Total for Section C			

Medication Regimen Complexity = Total (A) + Total (B) + Total (C)=

This regimen is derived from the article of George et al. (2004). [4]

Table S2: Example of a medication regimen complexity index calculation

Medication	**Component A**	**Component B**	**Component C**	**Total MRCI score**
aspirin 100 mg 1 tablet daily	1 (tablet)	1 (once daily)	0	
budesonide Turbuhaler 400 µg 2 puffs at midday	3 (turbuhaler)	1 (once daily)	1 (“multiple units”) + 1 (“specified times”)	
eformoterol Aerolizer 12 µg 2 puffs twice daily	3 (aerosol)	2 (twice daily)	1 (“multiple units”)	
ipratropium MDI 42 µg 2 puffs twice daily	4 (metered dose inhalator)	2 (twice daily)	1 (“multiple units”)	
simvastatin 20 mg 1 tablet each night	(already tablet counted)	1 (once daily)	1 (“specified times”)	
zolpidem 10 mg 1 tablet at night as needed	(already tablet counted)	0.5 (once daily prn)	1 (“specified times”)	
	11	**7.5**	**6**	**24.5**

Supplementary Table C

Dosage forms (needed for component A of the MRCI tool) were not included in the OPERAM database. The Dutch drug database "G-standaard" and the "NHG Standaard" inhalation guidelines were used to ascertain whether certain ATC codes could be linked to unique dosage forms within a given route of administration according to the MRCI tool.[14–16] These results are shown in table S3.

Table S3: Unique dosage forms per ATC code and route of administration

ATCODE	**Medication**	**Orale route of administration**	**Unit**
A01AB03	Chloorhexidine (mond- en keelmiddel)	gargle/mouthwashes	
A01AC02	Dexamethason	gargle/mouthwashes	
A01AD11	Tranexaminezuur (oromucosaal) | Tretinoïne (mondpasta)	gargle/mouthwashes	
N07BA01	Nicotine	gums/lozenges	
R05CB06	Ambroxol	gums/lozenges	
N02AB03	Fentanyl	gums/lozenges	
R02AX01	Flurbiprofen	gums/lozenges	
R02AA20	Lidocaïne/amylmetacresol/ dichloorbenzylalcohol	gums/lozenges	
A01AB04	Amfotericine B	gums/lozenges	
A06AB58	Picozwavelzuur/magnesiumoxide/ citroenzuur	powders/granules	
A06AC01	Psylliumzaad	powders/granules	
A06AC03	Sterculiagom	powders/granules	
A06AC51	Sennosiden/psylliumzaad	powders/granules	
A06AD13	Natriumsulfaat	powders/granules	
A06AD15	Macrogol	powders/granules	
A06AD65	Macrogol/elektrolyten	powders/granules	
A12AX	Calciumfosfaat/colecalciferol	powders/granules	
C10AC01	Colestyramine	powders/granules	
J01XX01	Fosfomycine	powders/granules	
N02BA15	Carbasalaatcalcium (bij pijn)	powders/granules	
N02BA51	Acetylsalicylzuur/metoclopramide	powders/granules	
V03AE01	Natriumpolystyreensulfonaat	powders/granules	
A02BX02	Sucralfaat	powders/granules	If not mL
A06AD12	Lactitol	powders/granules	If not mL
A07EB01	Cromoglicinezuur (systemisch)	powders/granules	If not mL
A02BA02	ranitidine	liquids	
A03AB02	Glycopyrronium **(oraal)**	liquids	

A03BA01	Atropine (systemisch)	liquids	
A06AB06	Sennosiden A+B	liquids	
A06AD10	Natrium-/kalium-/magnesiumsulfaat	liquids	
A06AD11	Lactulose	liquids	
A11CA01	Retinol	liquids	
A12CC03	Magnesiumgluconaat	liquids	
A12CE02	Natriumseleniet	liquids	
A12CX	Natriumfosfaat (bij hypofosfatemie)	liquids	
R05CA12	Klimopblad	liquids	
R05CB03	Carbocisteïne	liquids	
ATCODE	**Medication**	**Nasal route of administration**	
H04AA01	Glucagon	nasal drops/cream/ointment	
R01AX06	Mupirocine	nasal drops/cream/ointment	
R01AX10	Natriumchloride	nasal drops/cream/ointment	
ATCODE	**Medication**	**Transdermal route of administration**	
C01DA02	Nitroglycerine (transdermaal)	patches	
G04BD04	Oxybutynine	patches	
M02AA13	Ibuprofen (cutaan)	patches	
N01BB02	Lidocaïne (pleister)	patches	
N01BB20	Lidocaïne/tetracaïne	patches	
N02AB03	Fentanyl (transdermaal)	patches	
N02AE01	Buprenorfine	patches	
N04BC09	Rotigotine	patches	
N06DA03	Rivastigmine	patches	
N07BA01	Nicotine	patches	
D01AE13	Seleensulfide	paints/solutions	
D08AX07	Natriumhypochloriet	paints/solutions	
D11AF	Ditranol/salicylzuur	paints/solutions	
L04AD02	Tacrolimus	paints/solutions	
ATCODE	**Medication**	**Rectal route of administration**	
A06AG01	Natriumfosfaat (rectaal)	enemas	
A06AG10	Natriumdocusaat/sorbitol	enemas	
A06AG11	Natriumlaurylsulfoacetaat/ natriumcitraat/sorbitol	enemas	
A07EA06	Budesonide (maag-darmkanaal)	enemas	
A07EA07	Beclometason (bij darmontsteking)	enemas	

A09AA02	Pancreatine	enemas	
B05BA03	Glucose	enemas	
N03AE01	Clonazepam	enemas	
N05BA01	Diazepam	enemas	
N05CD08	Midazolam	enemas	
N05CX	Hypnotics and sedatives	enemas	
R03DA04	Theofylline	enemas	
V03AE01	Natriumpolystyreensulfonaat	enemas	
ATCODE	**Medication**	**Ocular route of administration**	
S01AA13	Fusidinezuur (bij ooginfectie)	eye gels/ointments	
S01AD03	Aciclovir (bij ooginfectie)	eye gels/ointments	
S01CA03	Hydrocortison/oxytetracycline/ polymyxine B (bij oogaandoening)	eye gels/ointments	
ATCODE	**Medication**	**Inhalator**	
R03AC03	Terbutaline	turbuhaler	
R03AL01	Fenoterol/ipratropium	metered dose inhalers	
R03BA08	Ciclesonide	metered dose inhalers	
R03AK11	Formoterol/fluticason	metered dose inhalers	
R03AL07	Glycopyrronium/formoterol	metered dose inhalers	
R03AL11	Formoterol/glycopyrronium/ budesonide	metered dose inhalers	
R03AC19	Olodaterol	nebuliser	
R03AL06	Tiotropium/olodaterol	nebuliser	
R03AL02	Salbutamol/ipratropium	nebuliser	
R03AK10	Vilanterol/fluticasonfuroaat	other DPIs	
R03AC18	Indacaterol	other DPIs	
R03AL03	Umeclidinium/vilanterol	other DPIs	
R03AL04	Indacaterol/glycopyrronium	other DPIs	
R03BB05	Aclidinium	other DPIs	
R03BB06	Glycopyrronium (inhalatie)	other DPIs	
R03BB07	Umeclidinium	other DPIs	
R03AL05	Aclidinium/formoterol	other DPIs	
R03AL08	Fluticason/umeclidinium/vilanterol	other DPIs	
R03AK14	Indacaterol/mometason	other DPIs	
R03AK12	Budesonide/salmeterol	aerolizer	

Supplementary Table D

Dosage forms (needed for component A of the MRCI tool) were not included in the OPERAM database. When an ATC code was available in multiple dosage forms, the dosage route and the dosage unit in the database were used to estimate the dosage form of the drug. In these cases, the most common dosage form within a dosage route was chosen to serve as the assumed dosage form (Table S4).

Table S4: The assumed dosage forms per dosage route noted in the OPERAM database

Dosage route OPERAM	**Dosage unit OPERAM**	**Assumed form of administration from MRCI, component A**
Per os		Capsule/tablet
Per os	ml	Liquids
Intervenous		Injections – Prefilled
Sublingual		Sublingual sprays/tabs
Subcutaneous		Injections – Prefilled
Nasal		Nasal spray
Transdermal		Creams / Gels / Ointments
Rectal		Suppositories
Inhaler		Metered dose inhaler
Nebulized		Nebuliser

Supplementary Table E

When the dosage route in the OPERAM database was coded under "other", the ATC-level was used to determine the assumed dosage form. The summary is given in table S5.[17]

Table S5: The assumed dosage forms of the "other" dosage route noted in the OPERAM database

(The prefix of the) ATC code	**Dosage interval OPERAM**	**Assumed form of administration from MRCI, component A**
S01-		Eye drops
S02-		Ear drops / creams / ointments
V03AN01 (oxygen)		Oxygen/Concentrator
B05D- B05ZA-		Dialysate
G02BB-		Pessaries
N02AA01 (morphine)	as directed	Patient controlled analgesia
G01A-		Vaginal creams

Supplementary Table F

Additional instructions for use (needed for component C) were not included in the data collection for the OPERAM study. We used label texts available in the G-standaard to determine whether certain additional instructions for use could be linked to ATC codes linked to an oral dosage route, regardless of the dosage form or the brand used. The label texts of the G Standaard which could contribute to the additional instructions for use according to the MRCI component C can be found in table S6.

Table S6: Label texts derived from the G Standaard which contribute to additional instructions for use according to the MRCI

Label text	**Additional instruction for use**
Kauwen of fijngemaakt met vocht innemen	break or crush tablet
Eerst uiteen laten vallen in water	dissolve tablet/powder
Eerst oplossen in water	dissolve tablet/powder
Water toevoegen aan poeder, schudden	dissolve tablet/powder
's Morgens innemen	take/use at specified times
's Avonds toedienen	take/use at specified times
's Avonds innemen	take/use at specified times
voor het slapen	take/use at specified times
Innemen op nuchtere maag	relation to food
Bij voorkeur 1 uur voor het eten innemen	relation to food
Ten minste een half uur VOOR het eten	relation to food
Bij voorkeur een half uur VOOR het eten	relation to food
Ten minste 15 minuten VOOR het eten	relation to food
Of 2 uur voor/na lunch/avondeten innemen	relation to food
Binnen 30 minuten na het eten innemen	relation to food
1 uur voor of 1 uur na het eten innemen	relation to food
Een half uur na het eten innemen	relation to food
Vlak VOOR het eten innemen	relation to food
2 uur voor en 1 uur na innemen niet eten	relation to food
Kort voor of tijdens het eten	relation to food
2 uur voor en 2 uur na innemen niet eten	relation to food
Ten minste 1 uur VOOR het eten innemen	relation to food
1 uur voor of 2 uur na het eten innemen	relation to food
Innemen met wat voedsel	relation to food
TIJDENS of vlak NA het eten innemen	relation to food
TIJDENS het eten innemen	relation to food
na de maaltijd	relation to food
Pas op met voedsel	relation to food
Niet met zuivel innemen, zie bijsluiter	take with specific fluid
met water innemen	take with specific fluid
Dosis verdunnen in een glas water	take with specific fluid
15 min. voor en na gebruik niet drinken	take with specific fluid

Innemen met veel vocht	take with specific fluid
Met water innemen, niet met melk	take with specific fluid
Bij dit middel GEEN grapefruit(sap) gebr.	take with specific fluid
Pas op met grapefruit, zie Apotheek.nl	take with specific fluid
Pas op met citrusfruit, zie Apotheek.nl	take with specific fluid
Gebruik volgens schema trombosedienst	take/use as directed
Zo lang gebruiken als arts voorschrijft	take/use as directed
Binnen 30 min. na inname niet gaan liggen	take/use as directed
Ten minste 1 uur VOOR het ontbijt	take/use at specified times + relation to food
Ten minste half uur VOOR ontbijt innemen	take/use at specified times + relation to food
Of ten minste een half uur voor ontbijt	take/use at specified times + relation to food
een half uur voor het ontbijt	take/use at specified times + relation to food
's Avonds innemen bij de maaltijd	take/use at specified times + relation to food
Zittend of staand innemen met veel water	take with specific fluid + take/use as directed

Supplementary Table G

The final version of the additional instructions for use linked to unique ATC codes in combination with the oral dosage route which we used in our code can be found in table S7.

Table S7: FInal version of ATC codes linked to additional instructions for use according to the MRCI

ATCODE	**Medication**	**Additional instruction for use**	**Unit**
A02AA04	Magnesiumhydroxide	break or crush tablet	
A02AD01	Algeldraat/ magnesiumhydroxide	break or crush tablet	If not mL
A02BC03	Lansoprazol	relation to food	
A02BX02	Sucralfaat	dissolve tablet/powder	If not mL
A02BX13	Alginezuur/ natriumwaterstofcarbonaat/ calciumcarbonaat	break or crush tablet	If not mL
A03FA03	Domperidon	relation to food	
A06AB02	Bisacodyl	take with specific fluid	
A06AB58	Picozwavelzuur/ magnesiumoxide/citroenzuur	dissolve tablet/powder	
A06AC01	Psylliumzaad	take with specific fluid	
A06AC01	Psylliumzaad	dissolve tablet/powder	
A06AC03	Sterculiagom	take with specific fluid	
A06AC03	Sterculiagom	dissolve tablet/powder	
A06AC51	Sennosiden/psylliumzaad	dissolve tablet/powder	
A06AC51	Sennosiden/psylliumzaad	take with specific fluid	
A06AD12	Lactitol	relation to food	
A06AD12	Lactitol	dissolve tablet/powder	If not mL
A06AD13	Natriumsulfaat	dissolve tablet/powder	
A06AD15	Macrogol	dissolve tablet/powder	
A06AD65	Macrogol/elektrolyten	dissolve tablet/powder	
A06AH03	Naloxegol	relation to food	
A06AH03	Naloxegol	take with specific fluid	
A07BA51	Medicinal charcoal, combinations	dissolve tablet/powder	
A07EB01	Cromoglicinezuur (systemisch)	dissolve tablet/powder	If not mL
A09AA02	Pancreatine	relation to food	
A10BA02	Metformine	relation to food	
A10BB01	Glibenclamide	relation to food	
A10BB03	Tolbutamide	relation to food	
A10BB09	Gliclazide	relation to food	
A10BB12	Glimepiride	relation to food	
A10BD07	Sitagliptine/metformine	relation to food	
A10BD08	Vildagliptine/metformine	relation to food	

A10BD20	Empagliflozine/metformine	relation to food	
A10BF01	Acarbose	relation to food	
A10BX02	Repaglinide	relation to food	
A12AX	Calciumfosfaat/colecalciferol	dissolve tablet/powder	
A12BA01	Kaliumchloride (oraal)	relation to food	
B01AA04	Fenprocoumon	take/use as directed	
B01AA04	Fenprocoumon	take/use at specified times + relation to food	
B01AA07	Acenocoumarol	take/use as directed	
B01AA07	Acenocoumarol	take/use at specified times + relation to food	
B01AC08	Carbasalaatcalcium (antitromboticum)	dissolve tablet/powder	
B01AC27	Selexipag	relation to food	
B01AE07	Dabigatran	take with specific fluid + take/use as directed	
B01AF01	Rivaroxaban	relation to food	15 mg, 20 mg
B02BX05	Eltrombopag	take with specific fluid	
B03AA02	Ferrofumaraat	relation to food	
B03AA02	Ferrofumaraat	take with specific fluid	
B03AA03	Ferrogluconaat	dissolve tablet/powder	
B03AA03	Ferrogluconaat	relation to food	
B03AA03	Ferrogluconaat	take with specific fluid	
B03AA07	Ferrosulfaat	relation to food	
B03AA07	Ferrosulfaat	take with specific fluid	
C01BC03	Propafenon	relation to food	
C01BD01	Amiodaron	relation to food	
C01BD01	Amiodaron	take with specific fluid	
C01EB17	Ivabradine	relation to food	
C01EB17	Ivabradine	take with specific fluid	
C03DB02	Triamtereen	relation to food	
C05CX03	Hippocastani semen	relation to food	
C07AB08	Celiprolol	relation to food	
C07AG01	Labetalol	relation to food	
C08CA02	Felodipine	take with specific fluid	
C08CA05	Nifedipine	take with specific fluid	
C08CA06	Nimodipine	take with specific fluid	
C08CA12	Barnidipine	take with specific fluid	
C08CA13	Lercanidipine	relation to food	
C08CA13	Lercanidipine	take with specific fluid	
C08DA01	Verapamil	take with specific fluid	
C08DB01	Diltiazem	take with specific fluid	

C09BB02	Enalapril/lercanidipine	relation to food	
C09BB02	Enalapril/lercanidipine	take with specific fluid	
C09XA52	Aliskiren/hydrochloorthiazide	take with specific fluid	
C10AA01	Simvastatine	take with specific fluid	
C10AA01	Simvastatine	take/use at specified times	
C10AA03	Pravastatine	take/use at specified times	
C10AA05	Atorvastatine	take with specific fluid	
C10AB02	Ciprofibraat	relation to food	
C10AB04	Gemfibrozil	relation to food	
C10AC01	Colestyramine	dissolve tablet/powder	
C10AX06	Omega-3-vetzuren	relation to food	
C10BA02	Ezetimib/simvastatine	take with specific fluid	
C10BA02	Ezetimib/simvastatine	take/use at specified times	
C10BA05	Ezetimib/atorvastatine	take with specific fluid	
G03BA03	Testosteron	relation to food	
G04CA04	Silodosine	relation to food	
G04CA52	Tamsulosine/dutasteride	relation to food	
G04CX02	Sabalis serrulatae fructus	relation to food	
H02AB04	Methylprednisolon	relation to food	
H03AA01	Levothyroxine	relation to food	
H03AA01	Levothyroxine	take with specific fluid	
H05BX01	Cinacalcet	relation to food	
J01AA08	Minocycline	take with specific fluid + take/use as directed	
J01CE02	Fenoxymethylpenicilline	relation to food	
J01CF05	Flucloxacilline	relation to food	
J01CR02	Amoxicilline met betalactamaseremmer	relation to food	
J01DB01	Cefalexine	relation to food	
J01DC02	Cefuroximaxetil	relation to food	
J01EE01	Cotrimoxazol	relation to food	
J01FA01	Erytromycine	relation to food	
J01MA02	Ciprofloxacine	take with specific fluid	
J01MA06	Norfloxacine	relation to food	
J01MA06	Norfloxacine	take with specific fluid	
J01XE01	Nitrofurantoïne	relation to food	
J01XX01	Fosfomycine	dissolve tablet/powder	
J01XX01	Fosfomycine	relation to food	
J02AC03	Voriconazol	relation to food	
J04AB02	Rifampicine	relation to food	
J04AC01	Isoniazide	relation to food	
J05AB14	Valganciclovir	relation to food	

J05AE03	Ritonavir	relation to food	
J05AE10	Darunavir	relation to food	
J05AG04	Etravirine	relation to food	
L01AA01	Cyclofosfamide	take with specific fluid	
L01AA01	Cyclofosfamide	take/use at specified times	
L01BB02	Mercaptopurine	take with specific fluid	
L04AD02	Tacrolimus (als immunosuppressivum)	relation to food	
L04AD02	Tacrolimus (als immunosuppressivum)	take with specific fluid	
L04AX01	Azathioprine	relation to food	
L04AX01	Azathioprine	take with specific fluid	
L01AX03	Temozolomide	relation to food	
L01BC06	Capecitabine	relation to food	
L02BG06	Exemestaan	relation to food	
L02BX03	Abirateron	relation to food	
L04AA18	Everolimus (bij transplantatie)	take with specific fluid	
L04AD01	Ciclosporine	take with specific fluid	
L04AX02	Thalidomide	take/use at specified times	
L04AX05	Pirfenidon	relation to food	
M01AB01	Indometacine (systemisch)	relation to food	
M01AB01	Indometacine (systemisch)	take with specific fluid + take/use as directed	
M01AB16	Aceclofenac	relation to food	
M01AB55	Diclofenac/misoprostol	relation to food	
M01AC06	Meloxicam	relation to food	
M01AE03	Ketoprofen	relation to food	
M01AE52	Naproxen/esomeprazol	relation to food	
M03BX01	Baclofen	relation to food	
M03BX04	Tolperison	relation to food	
M04AA01	Allopurinol	relation to food	
M04AB03	Benzbromaron	relation to food	
M04AC01	Colchicine	take with specific fluid	
M05BA01	Etidronic acid	relation to food	
M05BA01	Etidronic acid	take with specific fluid + take/use as directed	
M05BA02	Clodroninezuur	take with specific fluid + take/use as directed	
M05BA02	Clodroninezuur	relation to food	
M05BA04	Alendroninezuur	take with specific fluid	
M05BA04	Alendroninezuur	take/use as directed	
M05BA04	Alendroninezuur	take/use at specified times + relation to food	

M05BA06	Ibandroninezuur	take with specific fluid + take/use as directed	
M05BA06	Ibandroninezuur	take/use at specified times + relation to food	
M05BA07	Risedroninezuur	take with specific fluid + take/use as directed	
M05BA07	Risedroninezuur	take/use at specified times + relation to food	
M05BB03	Alendroninezuur/colecalciferol	take with specific fluid + take/use as directed	
M05BB03	Alendroninezuur/colecalciferol	take/use at specified times + relation to food	
N02AA05	Oxycodon	take with specific fluid	
N02AA55	Oxycodon/naloxon	take with specific fluid	
N02BA15	Carbasalaatcalcium (bij pijn)	dissolve tablet/powder	
N02BA51	Acetylsalicylzuur/ metoclopramide	dissolve tablet/powder	
N03AF01	Carbamazepine	relation to food	
N03AF01	Carbamazepine	take with specific fluid	
N03AG01	Valproïnezuur	relation to food	
N03AX09	Lamotrigine	dissolve tablet/powder	
N04AA02	Biperideen	relation to food	
N04BA02	Levodopa/benserazide	relation to food	
N04BA03	Levodopa/carbidopa/ entacapon	relation to food	
N04BB01	Amantadine	relation to food	
N05AH04	Quetiapine	take with specific fluid	
N05CD08	Midazolam	take with specific fluid	
N06AA04	Clomipramine	take with specific fluid	
N06AX22	Agomelatine	take/use at specified times	
N06DA02	Donepezil	take/use at specified times	
N06DA03	Rivastigmine	relation to food	
N07AA03	Distigmine	relation to food	
N07AX01	Pilocarpine (mond- en keelmiddel)	relation to food	
N07BA01	Nicotine	take with specific fluid	
N07XX07	Fampridine	relation to food	
P01AX06	Atovaquon	relation to food	
P01BA02	Hydroxychloroquine	relation to food	
P02CA03	Albendazol	relation to food	
R03DA04	Theofylline	relation to food	
R03DC03	Montelukast	take/use at specified times	
R06AX26	Fexofenadine	take with specific fluid	

V03AE01	Natriumpolystyreensulfonaat	dissolve tablet/powder	
V03AE02	Sevelameer	relation to food	
V03AE03	Lanthaancarbonaat	relation to food	
V03AE04	Calciumacetaat/ magnesiumcarbonaat	relation to food	
V03AE07	Calciumacetaat	relation to food	

Supplementary Table H

A selection of six regimens from George et al. was used for a second validation for our coded MRCI script.[4] The original regimens are given in the left column of Table S8. The translation of these regimens into their respective equivalents in the OPERAM database format are given in the right column of Table S8.

Table S8 Regimens of George's validation set and their respective equivalents according to the OPERAM database format

Regimens of George's validation set	**The respective equivalents according to the OPERAM database format**
Regimen A albuterol MDI 100 µg 2 puffs each morning	**Regimen A** R03AC02 once daily 200 µg inhalation route
Regimen B albuterol MDI 100 µg 2 puffs as needed flunitrazepam 1 mg 1/2 tablet each night fluticasone MDI 125 µg 2 puffs twice daily ipratropium MDI 42 µg 2 puffs 3 times daily	**Regimen B** R03AC02 once daily prn 200 µg inhalation route N05CD03 once daily 0.5 mg oral route R03BA05 twice daily 250 µg inhalation route R03BB01 three times daily 84 µg inhalation route
Regimen C aspirin 100 mg 1 tablet daily budesonide Turbuhaler 400 µg 2 puffs at midday eformoterol Aerolizer 12 µg 2 puffs twice daily ipratropium MDI 42 µg 2 puffs twice daily simvastatin 20 mg 1 tablet each night zolpidem 10 mg 1 tablet at night as needed	**Regimen C** N02BA01 once daily 100 mg oral route R03BA02 once daily 800 µg inhalation route R03AC13 twice daily 24 µg inhalation route R03BB01 twice daily 84 µg inhalation route C10AA01 once daily 20 mg oral route N05CF02 once daily prn 10 mg oral route
Regimen D albuterol MDI 100 µg 1 puff as needed albuterol nebules 2.5 mg/2.5 mL 1 each morning and afternoon alendronate sodium 5 mg 1 tablet weekly fluticasone MDI 125 µg 1 puff twice daily furosemide 40 mg 1 tablet twice daily ibuprofen 400 mg 1 tablet twice daily ipratropium nebules 250 µg/mL 1 each morning and afternoon perindopril 4 mg 1 tablet each morning	**Regimen D** R03AC02 once daily prn 100 µg inhalation route R03AC02 twice daily 2.5 mg nebulished M05BA04 once a week 5 mg oral route R03BA05 twice daily 125 µg inhalation route C03CA01 twice daily 40 mg oral route M01AE01 twice daily 400 mg oral route R03BB01 twice daily 250 µg inhalation route C09AA04 once daily 4 mg oral route

potassium chloride 600 mg SR 1 tablet twice daily	A12BA01 twice daily 600 mg oral route
theophylline 300 mg SR 1 tablet twice daily	R03DA04 twice daily 300 mg oral route
Regimen E	**Regimen E**
albuterol MDI 100 µg 1–2 puffs every 4–6 hours	R03AC02 100 µg six times daily inhalation route
albuterol nebules 2.5 mg/2.5 mL 1 twice daily	R03AC02 twice daily 2.5 mg nebulished
doxycycline 50 mg 1 tablet daily after food	J01AA02 once daily 50 mg oral route
fluticasone plus salmeterol Accuhaler 500/50 µg 1 puff twice daily	R03AK06 twice daily 500 µg inhalation route
ipratropium MDI 42 µg 1–2 puffs every 4–6 hours	R03BB01 six times daily 42 µg inhalation route
ipratropium nebules 500 µg/mL 1 twice daily	R03BB01 twice daily 500 µg nebulished
medroxyprogesterone 10 mg tablets, use as directed	G03DA02 as directed 10 mg oral route
estradiol 50 µg 1 patch each week	G03CA03 once a week 50 µg transdermal route
pantoprazole 40 mg 1 tablet daily	A02BC02 once daily 40 mg oral route
piroxicam 10 mg 1 capsule as needed	M01AC01 once daily prn 10 mg oral route
Regimen F	**Regimen F**
acetaminophen 500 mg 2 tablets 4 times daily	N02BE01 four times daily 1000 mg oral route
albuterol MDI 100 µg 2 puffs as needed	R03AC02 once daily prn 200 µg inhalation route
albuterol nebules 2.5 mg/2.5 mL 1 puff 4 times daily	R03AC02 four times daily2.5 mg nebulished
alendronate sodium 70 mg 1 tablet weekly	M05BA04 once a week 70 mg oral route
amitriptyline 50 mg 1 tablet each night	N06AA09 once daily 50 mg oral route
atorvastatin 10 mg 1 tablet each night	C10AA05 once daily 10 mg oral route
colchicine 0.5 mg 1 tablet daily	M04AC01 once daily 0.5 mg oral route
digoxin 250 µg 1 tablet daily	C01AA05 once daily 250 µg oral route
doxycycline 100 mg 1 tablet each morning	J01AA02 once daily 100 mg oral route
ergocalciferol 25 µg 1 capsule daily	B05XC once daily 25 µg oral route
ferrous sulfate plus folic acid 1 tablet daily	B03AD03 once daily 1 unit oral route
fluticasone MDI 250 µg 2 puffs twice daily plus salmeterol MDI 25 µg 2 puffs twice daily (separate inhalers) or fluticasone plus salmeterol MDI 250/25 µg 2 puffs twice daily (1 inhaler)	R03AK06 twice daily 250 µg inhalation route
furosemide 40 mg 2 tablets twice daily	C03CA01 twice daily 80 mg oral route
gliclazide 80 mg 3 tablets each morning	A10BB09 once daily 240 mg oral route
human insulin injection 3 mL, use as directed	A10AB05 as directed
ipratropium MDI 42 µg 1 puff 4 times daily	R03BB01 four times daily 42 µg inhalation route
ipratropium nebules 250 µg/mL 1 puff 4 times daily	R03BB01 four times daily 250 µg inhalation route
levodopa plus benserazide 100/25 mg 1 tablet each morning and 2 tablets at midday	N04BA02 twice daily 125 mg oral route
metformin 500 mg 2 tablets twice daily	A10BA02 twice daily 1000 mg oral route

pantoprazole 40 mg 1 tablet daily	A02BC02 once daily 40 mg oral route
prednisolone 5 mg 1 tablet twice daily	H02AB06 twice daily 5 mg oral route
sertraline 50 mg 1 tablet each morning	N06AB06 once daily 50 mg oral route
spironolactone 25 mg 1 tablet at lunch	C03DA01 once daily 25 mg oral route
warfarin tablets, use as directed	B01AA03 as directed

MDI = metered-dose inhaler; SR = sustained release.