SCHOLZ DataBank

ADR Control Panel (ADR CP)

User Manual

Version 1.01
February 1st, 2025

Summary of the features of the SCHOLZ Databank ADR CP:

- highly innovative and dynamic drug drug interaction checker
- provides the "all in one" overview of drug risks in a patient medication
- reconciles multiple kinetic interactions and adverse drug effects
- e²CP technology visualizes alerts and makes medication errors transparent at one glance
- multiple e²CP technology: paves the way for the doctor's fast track to find safe polypharmacy prescriptions for multimorbide patients within seconds
- Quattro Optimizer to find safer polypharmacy prescriptions for multimorbide patients
- interface to EMR- and E-prescribing software
- based on prescriber information, literature and FDA interaction guide lines
- RXCUI, NDCCODE and Surescripts approved drug database interface for e-prescribing available
- More than 40 years proven experience in the development of drug interaction checkers

The ADR CP is available on https://adrcp.scholzdatabank.com/

**Please ask for your credentials to use the ADR CP
and write to support@scholzdatabank.com .**

Introduction to the ADR Control Panel (ADR CP) including a Patient Case

The **ADR CP** is the "all in one" representation of adverse drug risks which helps the user to keep the overview over kinetic drug interactions and dynamic adverse drug reactions and thereby take the fast track to drug safety and avoidance of serious medication errors when prescribing. The core of the **ADR CP** consists of a highly innovative and dynamic literature based drug interaction checker which reconciles the control of **MDDI** (Multi-Drug Drug Interactions) and **ADR** (Adverse Drug Risks) in a patient medication. Thereby, the **ADR CP** makes the impact of kinetic and dynamic drug interactions on vital signs and adverse drug risks of major importance transparent and recognizable at one glance.

The following screen presents the empty **ADR CP** before entering drugs of a Medication or transmitting the drugs from an EMR- or E-prescribing software:

Screen :

ADR CP Version 1.0 provides the following functions in the main screen:

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- Account: In the Top Right corner of the screen is the User Account details. User name initials are visible there. Right next to it is a drop-down menu. The User can log out using this option.
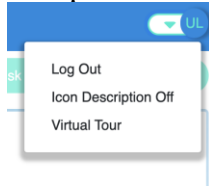
User can also turn off/turn on Icon Description using the given option.

- Drugs: may be added (+) or deleted (-)

  o The position of the medicine added is dependent on the clicked button position. add (+) and delete (-) buttons are present on the header row right next to Total ADR

or you can hover over each drug name to view these buttons.

  - Add button present in the header row will always add medicine to the bottom of the list.

  - Delete button present in the header will remove all the drugs in the current Medication and all other Medications and also reset the optimizer. clicking this button shows the warning message: "This will delete all your drugs & reset the optimizer. Are you sure?". click OK to delete all drugs.

  - Add and delete buttons that show on each drug row affect individual rows.

    - Add (+) button add the new drug below the clicked button. When a new drug is added, index numbers are updated. Add button on MULTAQ 400 MG Oral Tablet" added the "Panadol Extra Strength 500 MG Oral Tablet" below it.

Total ADR: ~ 22%	ADR / Drug: ~ 7.22%	➕ ➖	MDDI
1	MULTAQ 400 MG Oral Tablet ⊡ ➕ ➖		
2	Panadol Extra Strength 500 MG Oral Tablet		
3	simvastatin 80 MG Oral Tablet		DI

- Delete button removes the individual row on which the button (-) is clicked. e.g. clicking on the delete button on the row number 1 will delete it. Warning message: "This will delete the MULTAQ 400 MG ORAL TABLET and recalculate the results. Are you sure?" will be shown for confirmation. Click OK to delete the drug.

- The ADRCP is refreshed on add, delete, or updated operations. New calculations are performed and results are updated according to the new drug list.

- Info tab is present right next to the Operations tab. clicking this button will open up the MDDI Levels guidance.
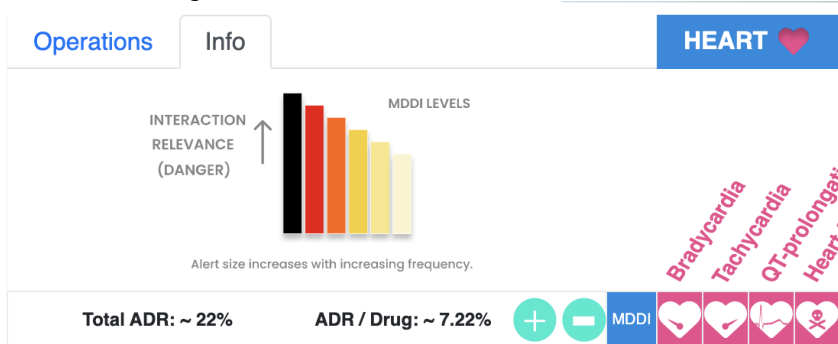
- Operations Tab is the default selected tab. It has an Optimizer button and Traffic lights for Drug Interactions (DI) and – not yet active in ADR CP 1.0 - for Contraindications (CI), After Effects (AE), and Drug Allergies (AL).
Traffic lights are clickable buttons that also act as indicators. These have Green, Yellow, and Red Traffic lights. By default No light is visible and the ADR summary panel is empty/blank.
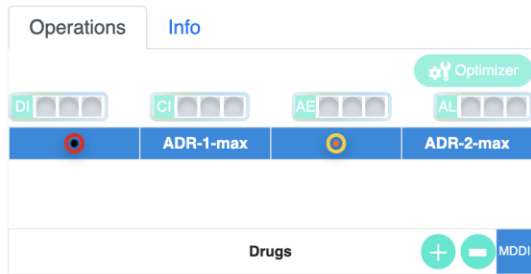
Adding one drug will show values in ADR summary Panel; please note the tilde in front of the % values indicating that all values are approximate assessments. Adding more than one drug will update the ADR summary panel, and turn on the traffic lights according to the

results.

Below the Traffic lights is the ADR summary panel.

- ADR CP shows loaders when a component is loading. One loader is visible at the bottom right corner of the screen. it becomes visible when any component is loading or some calculations are being performed. The second loader appears in the relevant components for example if DI(Traffic light) is loading then you can observe the following screen.

- ADR: with each drug entered the e²CP function (see below) is activated and presents the **ADR CP** with the **MDDI** alerts for the drug drug interactions and the **ADR** warning lights for the adverse reactions related to the drugs. The organ sorted table contains 31 side effects that are related to vital signs or serious potential adverse effects which should be avoided.

- Optimizer: when more than 2 drugs are entered the Optimizer function can be used.

- Literature for relevant drugs/ drugs involved can be viewed using the literature button(icon: a medical book) where available.

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- The taskbar at the footer (bottom of the screen) provides access to the introductory user manual and legal information you should know when using the **ADR CP**.

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*Please look at the **ADR CP** for the fictitious patient Willy Nottingham in screen 1 below:*

*Willy Nottingham is an elderly multimorbide patient. He suffers from severe cardiac arrhythmia, hypertension, and cholesterolemia. He suffers also from a Major Depressive Disorder (MDD) and in these days from an acute bacterial bronchitis which requires antibiotic treatment. Basically each drug listed might be appropriate to treat a specific disease or condition of Willy Nottingham. But what about the multiple mutual impacts and possible adverse effects? The **ADR CP** of SCHOLZ Databank helps to answer these questions.*

Screen 1:
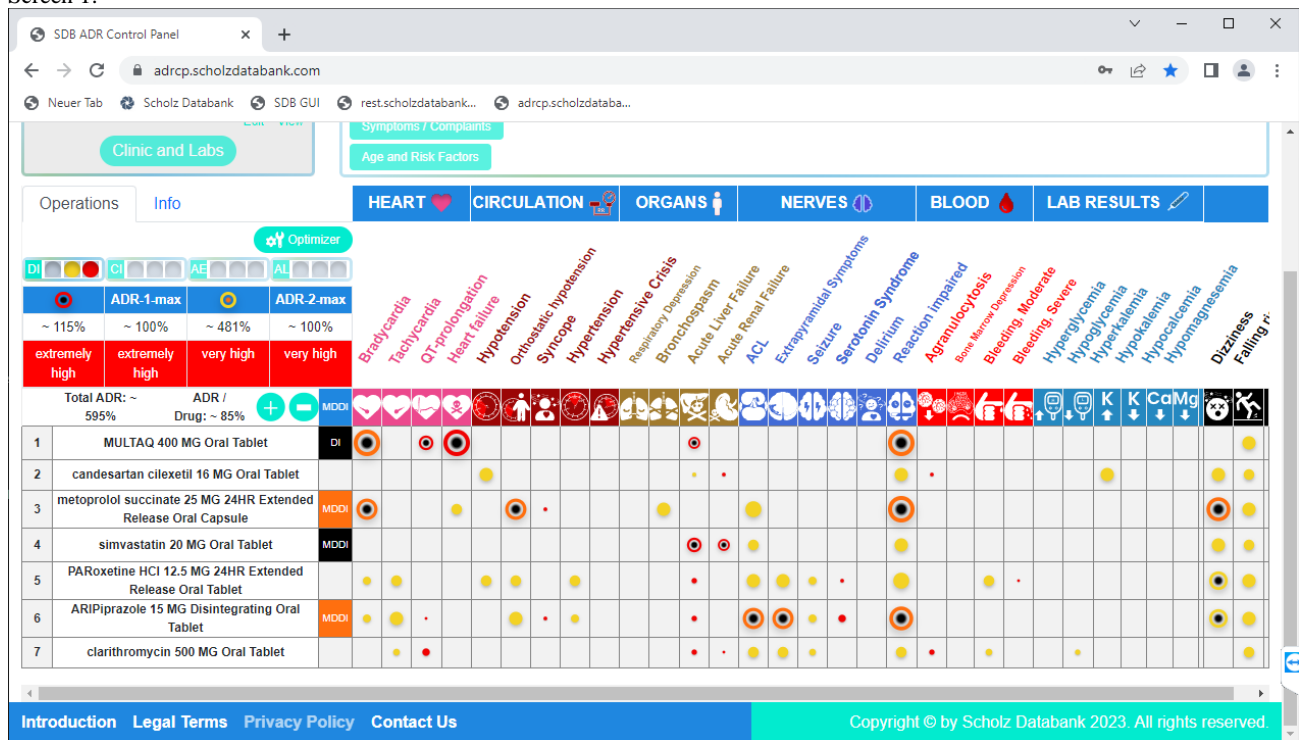
The new **e²CP technology** ("electronic express ChromaPictography") provides the **ADR CP** even for complex medications as chromapictogram within seconds. It reminds of running chromatograms in a chemist's lab, however with very high speed and performance.

The special alerts stand for: **DI** = classical drug drug interactions; **MDDI** = multi(ple) drug drug interactions; **Lights in the Table** = warnings for dangerous = ADR-1 adverse effects (colors: red,

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red-black) or important = ADR-2 adverse effects (colors: yellow, yellow-black) as sorted by organs. More details are described in the following chapters.

The adverse drug risks focussed on in the **ADR CP** table may be dependent on the magnitude of the (multi) drug drug interactions detected. They are in particular related to the vital signs and serious drug side effects as listed in the **ADR CP** main screen. Size and color of the ADR alerts in the cells visualize the relevance and frequency of the adverse effects.

When clicking on the **DI** or **MDDI** alerts or the **warning lights** in the table **DI**, **MDDI** or **ADR** protocols can be retrieved as a short report.

*Clarithromycin is evidently not appropriate to treat the acute bacterial infection in this scenario. Comparing screen 2 (without clarithromycin) and screen 1 (with clarithromycin) shows, that clarithromycin causes especially severe **MDDIs** with dronedarone/Multaq and simvastatin; it has also an important additional impact on aripiprazole, see screens 3, 4, and 5. These impacts mirror also in the big differences of the risk scores displayed such as the Total ADR as well as the ADR-1-max and ADR-2max, representing the approximate assessments of especially serious side effects such as Heart Failure or less serious side effects such as Hypotension.*

Screen 2:

SDB ADR Control Panel

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Aktualisieren

Neuer Tab   Scholz Databank   SDB GUI   rest.scholzdatabank...   adrcp.scholzdataba...

Mr. Demo Patient
Edit   View
Clinic and Labs

Diagnoses Name
Symptoms / Complaints
Age and Risk Factors

	HEART ♥	CIRCULATION	ORGANS	NERVES	BLOOD 🩸	LAB RESULTS ✎

Operations   Info

Optimizer

DI ⬤⬤⬤   CI ▢▢▢   AE ▢▢▢   AI ▢▢▢

⦿	ADR-1-max	⦿	ADR-2-max
~ 11.9%	~ 11.0%	~ 341%	~ 100%
extremely high	extremely high	very high	very high

Total ADR: ~ 353%   ADR / Drug: ~ 59%   + −   MDDI

Column headers (rotated): Bradycardia, Tachycardia, QT-prolongation, Heart failure, Hypotension, Orthostatic hypotension, Syncope, Hypertension, Hypertensive Crisis, Respiratory Depression, Bronchospasm, Acute Liver Failure, Acute Renal Failure, ACL, Extrapyramidal Symptoms, Seizure, Serotonin Syndrome, Delirium, Reaction Impaired, Agranulocytosis, Bone Marrow Depression, Bleeding, Moderate, Bleeding Severe, Hyperglycemia, Hypoglycemia, Hyperkalemia, Hypokalemia, Hypocalcemia, Hypomagnesemia, Dizziness, Falling

#	Drug		
1	MULTAQ 400 MG Oral Tablet		
2	candesartan cilexetil 16 MG Oral Tablet		
3	metoprolol succinate 25 MG 24HR Extended Release Oral Capsule	MDDI	
4	simvastatin 20 MG Oral Tablet	DI	
5	PARoxetine HCl 25 MG 24HR Extended Release Oral Tablet		
6	ARIPiprazole 20 MG Oral Tablet	MDDI	

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The following screen 3 illustrates the **DI** impact of clarithromycin on the metabolism of dronedarone and the increase of the drug exposure (AUC) to approximately 6.7-fold.

Screen 3:

Parameter	Description	Relative Value	Relative Change
F	Bioavailability about	~ 280%	~ 182%
AUC	Area under the curve about	~ 670%	~ 570%

The (relative) AUC of DRONEDARONE is due to the enzyme inhibition or function impairment assessed to be about ~ 670% of the normal.
A dose reduction up to ~ 85% could be indicated (desired Booster-effects exempted).
A normal renal function/CKD Stage 1 with a renal Clearance of 100.00 ml/min is assumed.

The Therapeutic Index of DRONEDARONE is low.
Please note: Assessments are usually made under the assumption of linear kinetics (first order kinetics)! Assessments relate to the ingredients declared; relevant active metabolites are assigned to the total active moiety represented by the ingredient, if possible. Any change of dosing has to take place under control of vital signs and relevant clinical and lab parameters as well as under regard of the prescriber information and strengths and dosage forms available. Dose reductions of more than 75% are usually not recommended, and in such cases a substitution of drugs involved is preferred.
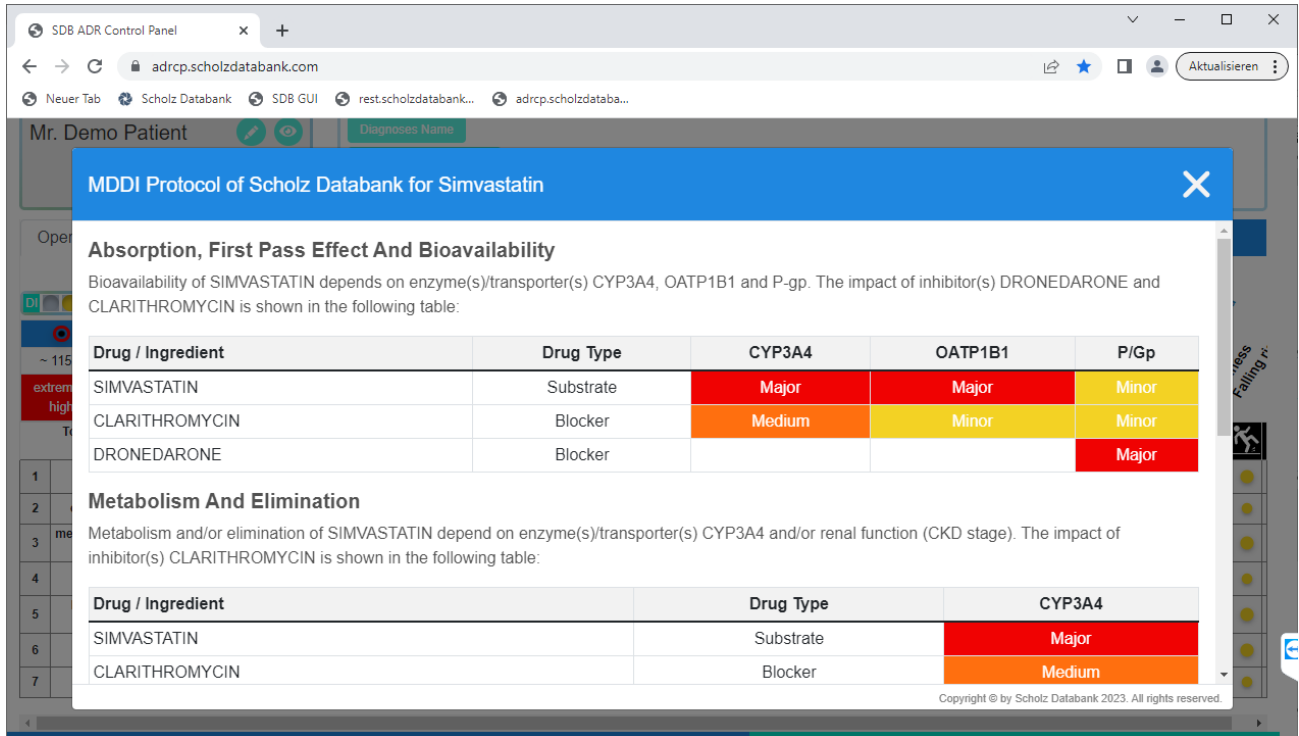
Sources and Literature

Information of SCHOLZ Databank - the drug reference tool for drug information and interactions since 1981 © All rights reserved, SCHOLZ DATABANK Inc., USA, 2023

The following screens 4a and 4b illustrate the dual **MDDI** impact of clarithromycin and dronedarone on the metabolism of simvastatin and the increase of the drug exposure (AUC) to approximately the 12-fold.

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Screen 4a:

MDDI Protocol of Scholz Databank for Simvastatin

Absorption, First Pass Effect And Bioavailability

Bioavailability of SIMVASTATIN depends on enzyme(s)/transporter(s) CYP3A4, OATP1B1 and P-gp. The impact of inhibitor(s) DRONEDARONE and CLARITHROMYCIN is shown in the following table:
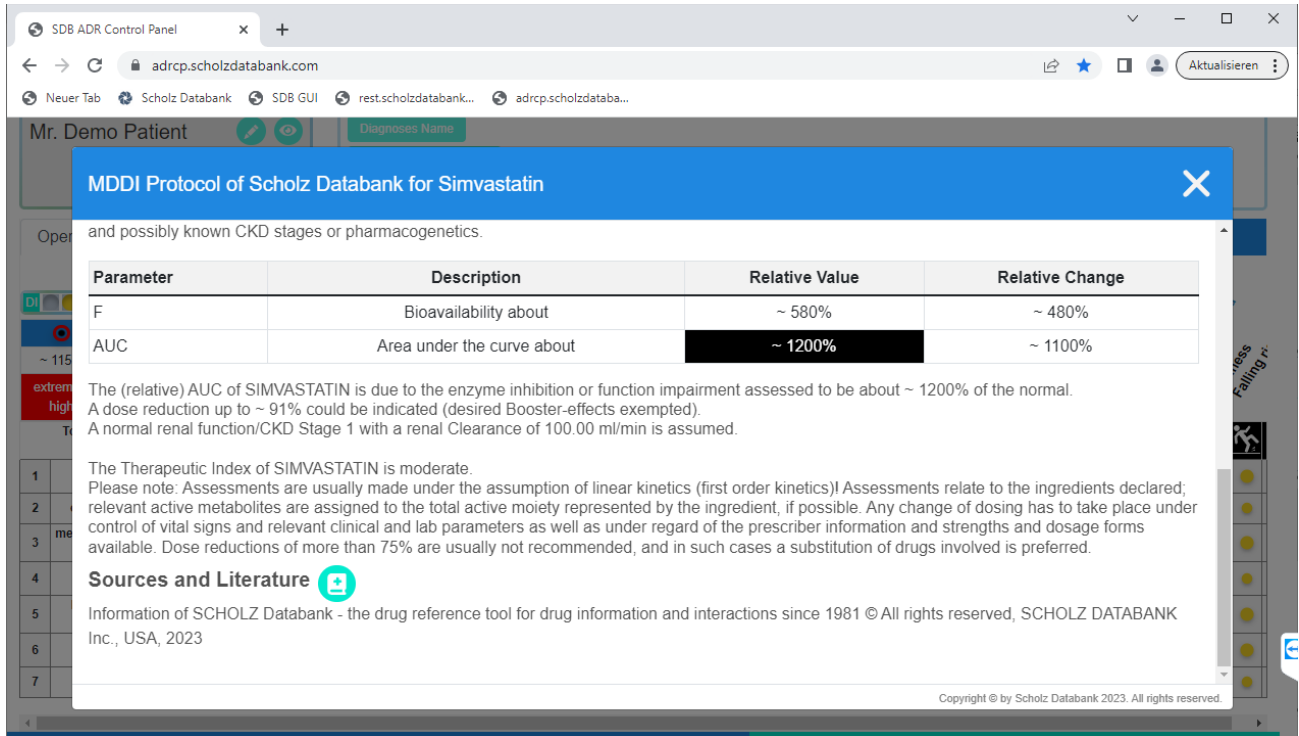
Drug / Ingredient	Drug Type	CYP3A4	OATP1B1	P/Gp
SIMVASTATIN	Substrate	Major	Major	Minor
CLARITHROMYCIN	Blocker	Medium	Minor	Minor
DRONEDARONE	Blocker			Major

Metabolism And Elimination

Metabolism and/or elimination of SIMVASTATIN depend on enzyme(s)/transporter(s) CYP3A4 and/or renal function (CKD stage). The impact of inhibitor(s) CLARITHROMYCIN is shown in the following table:

Drug / Ingredient	Drug Type	CYP3A4
SIMVASTATIN	Substrate	Major
CLARITHROMYCIN	Blocker	Medium

Screen 4b:

MDDI Protocol of Scholz Databank for Simvastatin

and possibly known CKD stages or pharmacogenetics.

Parameter	Description	Relative Value	Relative Change
F	Bioavailability about	~ 580%	~ 480%
AUC	Area under the curve about	~ 1200%	~ 1100%

The (relative) AUC of SIMVASTATIN is due to the enzyme inhibition or function impairment assessed to be about ~ 1200% of the normal.
A dose reduction up to ~ 91% could be indicated (desired Booster-effects exempted).
A normal renal function/CKD Stage 1 with a renal Clearance of 100.00 ml/min is assumed.

The Therapeutic Index of SIMVASTATIN is moderate.
Please note: Assessments are usually made under the assumption of linear kinetics (first order kinetics)! Assessments relate to the ingredients declared; relevant active metabolites are assigned to the total active moiety represented by the ingredient, if possible. Any change of dosing has to take place under control of vital signs and relevant clinical and lab parameters as well as under regard of the prescriber information and strengths and dosage forms available. Dose reductions of more than 75% are usually not recommended, and in such cases a substitution of drugs involved is preferred.
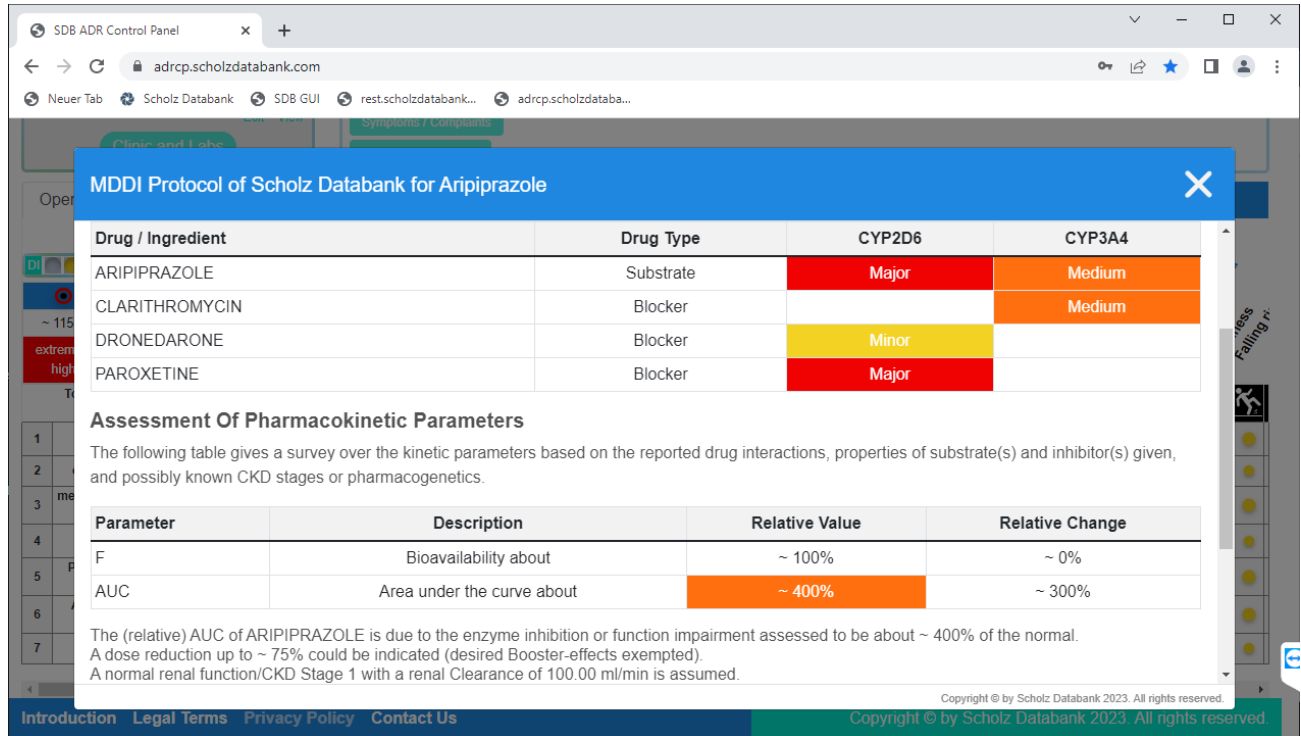
Sources and Literature

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The following screen 5 illustrates the dual **MDDI** impact of paroxetine and clarithromycin on the metabolism of aripiprazole at enzymes CYP2D6 and CYP3A4 and the increase of the drug exposure (AUC) to approximately the 4-fold.

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Screen 5:

If you want to learn more details about the **MDDI** technology please read the special chapter below:

MDDI: Assessing at one glance how one drug might be affected by ALL other drugs of the medication

Vital Signs and Major Serious Side Effects analyzed

The **ADR CP** has its focus on the following adverse/side effects:
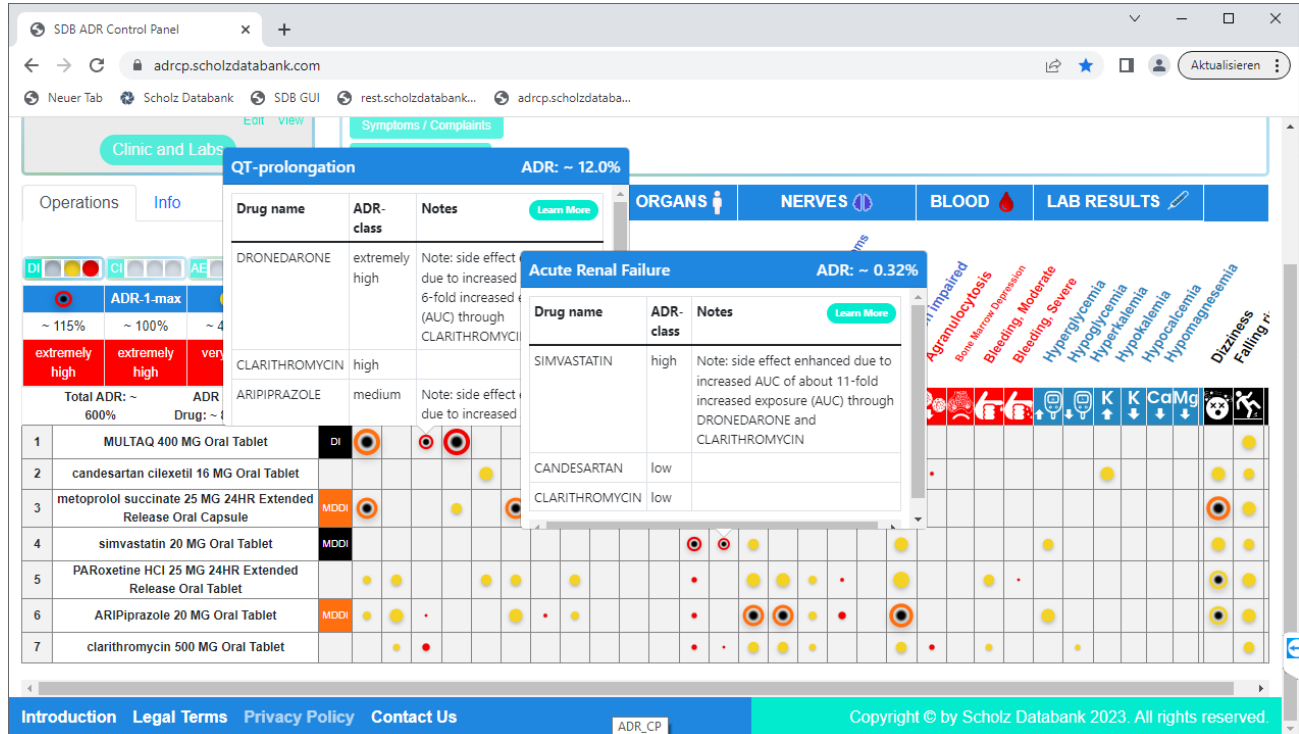
QT interval prolongation, **bradycardia, tachycardia,** *heart failure*, **hypertension, hypotension,** *syncope*, *respiratory depression*, **bronchospasm,** *acute hepatic failure*, *acute renal failure*, *seizure*, **extrapyramidal symptoms,** *serotonin syndrome*, **reaction time impaired, anticholinergic burden,** *severe* **and moderate** *bleeding*, *agranulocytosis,* **hypoglycemia, hyperglycemia, hypokalemia, hyperkalemia, hypomagnesemia, dizziness, falling risk.** *Terms in italic writing are usually classified as dangerous adverse effects, represented also by ADR-1 and ADR-1-max values.*

Thereby vital signs and major serious side effects may be effectively controlled. The **ADR CP** may be supplemented in the future by additional side effects. As the computation of all multiple drug drug interaction and side effects with their ADRs is very complex limits are only set by the hardware capabilities and high

performance computers (HPC) are needed to process user requests in user friendly response times. This applies in particular when optimizing of medications is the target as described in the next chapter.

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In the case of Willy Nottingham the potential clinical results due to the pharmacokinetic and pharmacodynamic interactions can be retrieved in short protocols, for example for dronedarone/Multaq or simvastatin. In particular unacceptably high ADRs for dronedarone and its side effects QT prolongation or Heart Failure and for simvastatin and its side effects acute Liver or Renal Failure make clear that the medication has to be adapted and optimized to avoid severe harm to the patient, see for example screens 6.

Screen 6:

If you want to learn more details about the ADR assessment please read the special chapter below:

General Rulings how the ADR CP works

*The **ADR CP** develops its power, especially in complex polypharmacy scenarios and when treating multimorbide elderly patients. For this purpose, it provides the Quattro Optimizer function, and we shall see in the following chapter how a medication containing dronedarone/Multaq, simvastatin, and clarithromycin can be improved.*
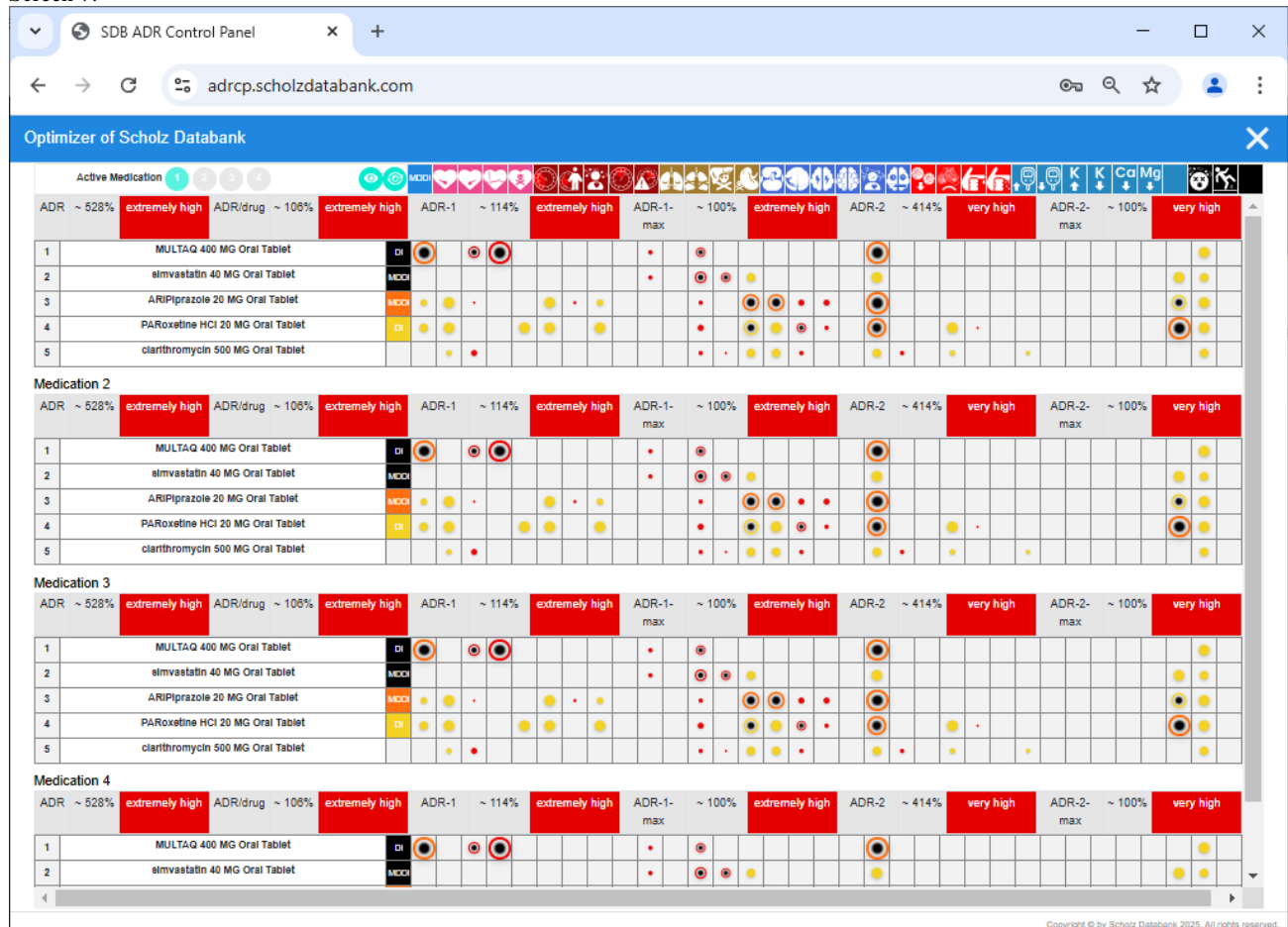
Optimizing Medications: The ADR CP as the fast track in polypharmacy to find safer medications!

By using the new technology of providing multiple e²CPs the productivity to find better solutions for complex polypharmacy prescriptions may be tremendously enhanced and improved.

ADR CP 1.0 helps the user to compare up to four different medications and - by substituting drugs causing serious adverse risks – to find alternative medication scenarios with less risk.

When clicking the Optimizer Button the complete medication of the main screen is presented in the Quattro Optimizer screen in Medication 1 but also in Medication 2, Medication 3, and Medication 4.

Screen 7:

Medication 1 remains always as the original medication which shall be optimized.
Selected Medication is marked with a check/tick sign. Medication added to Selected Medication also appears automatically in the ADR CP main panel while adding a drug to non-selected Medications is only visible in

Optimizer.
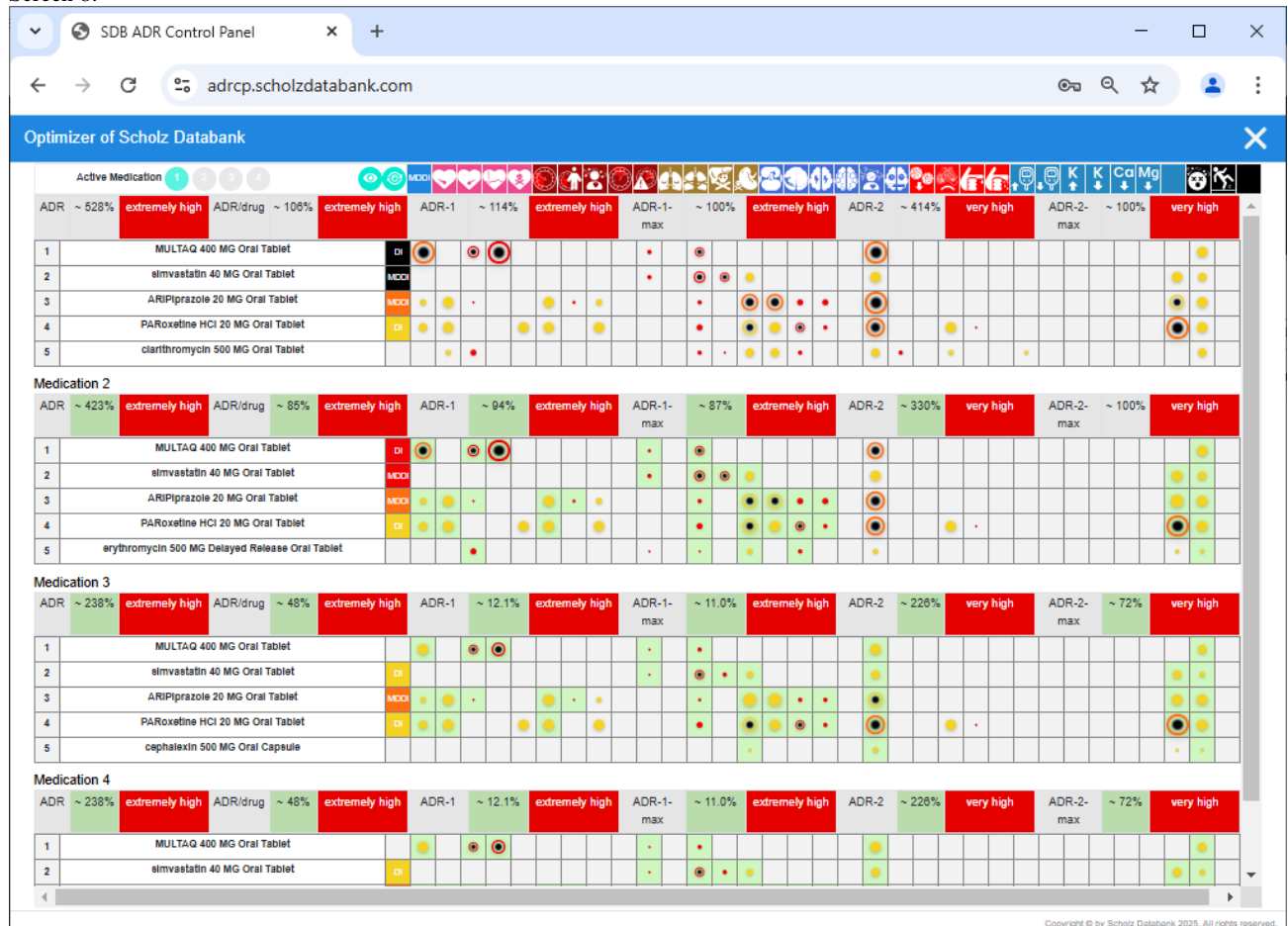
Medication 2, 3, and 4 can be adapted by adding, deleting or substituting the drugs;

they can all at any time send to the main screen by clicking on the matching Check in the header line. Adaptations and substitutions of medications require medical-pharmaceutical expertise of the user; future versions of the ADR CP shall be supported additionally by automated processes to find and compare similar drugs appropriate for the purposes desired.

The simulation of different scenarios is efficiently supported as values for the ADR, ADR/drug, ADR-1, ADR-1-max, ADR-2, and ADR-2-max are updated with each change in a scenario and Medications 1, 2, 3, and 4 can be compared accordingly, see screen 8. Ideally ADR-1-max should be <= 0.1% and ADR-2-max <= 10%.

Screen 8:

SDB ADR Control Panel — adrcp.scholzdatabank.com

Optimizer of Scholz Databank

Active Medication 1 2 3 4

ADR ~ 528% extremely high | ADR/drug ~ 106% extremely high | ADR-1 ~ 114% extremely high | ADR-1-max ~ 100% extremely high | ADR-2 ~ 414% very high | ADR-2-max ~ 100% very high

1. MULTAQ 400 MG Oral Tablet — DI
2. simvastatin 40 MG Oral Tablet — MDDI
3. ARIPiprazole 20 MG Oral Tablet — MDDI
4. PARoxetine HCl 20 MG Oral Tablet — DI
5. clarithromycin 500 MG Oral Tablet

Medication 2

ADR ~ 423% extremely high | ADR/drug ~ 85% extremely high | ADR-1 ~ 94% extremely high | ADR-1-max ~ 87% extremely high | ADR-2 ~ 330% very high | ADR-2-max ~ 100% very high

1. MULTAQ 400 MG Oral Tablet — DI
2. simvastatin 40 MG Oral Tablet — MDDI
3. ARIPiprazole 20 MG Oral Tablet — MDDI
4. PARoxetine HCl 20 MG Oral Tablet — DI
5. erythromycin 500 MG Delayed Release Oral Tablet

Medication 3

ADR ~ 238% extremely high | ADR/drug ~ 48% extremely high | ADR-1 ~ 12.1% extremely high | ADR-1-max ~ 11.0% extremely high | ADR-2 ~ 226% very high | ADR-2-max ~ 72% very high

1. MULTAQ 400 MG Oral Tablet
2. simvastatin 40 MG Oral Tablet — DI
3. ARIPiprazole 20 MG Oral Tablet — MDDI
4. PARoxetine HCl 20 MG Oral Tablet — DI
5. cephalexin 500 MG Oral Capsule

Medication 4

ADR ~ 238% extremely high | ADR/drug ~ 48% extremely high | ADR-1 ~ 12.1% extremely high | ADR-1-max ~ 11.0% extremely high | ADR-2 ~ 226% very high | ADR-2-max ~ 72% very high

1. MULTAQ 400 MG Oral Tablet
2. simvastatin 40 MG Oral Tablet — DI

Substitution by erythromycin reduces the major kinetic **MDDI** interactions caused by clarithromycin, however, as displayed in screen 8 for Medication 2, there is furthermore a substantial increase of the dronedarone induced risk of QT prolongation which should be avoided; therefore cephalexin instead of the macrolides would be the better choice and it does not show any impact on the QT interval as also displayed in screen 8 for Medication 3. Substitution by the alternate cephalosporine cefaclor or the penicillin amoxicillin would yield similarly reduced ADR values.

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General Rulings how the ADR CP works

When you enter or delete a drug in the drug listing by clicking the green „+" or „-" button and have selected a special item for the listing the (multiple) drug drug interactions and the ADR over all 31 slanted listed side effects are assessed and the ADR displayed as Total ADR and ADR/Drug in %. As already pointed out: the tilde in front of the % values indicates that all values are approximate assessments.

The ADR (Adverse Drug Risk) for an adverse effect or side effect is the risk in % based on the occurrence and frequency of the side effect and related side effects at normal therapy and dosing of the drug(s) involved. It may have values from 0 to 100% for a single ADR as a function of the relative dose (Doserel: default average value = 0.5 and maximum value = 1) including overdosage due to MDDI kinetics and a defined basic ADR, for example as shown in the diverse following graphs:

$$ADR = f(Doserel, basic\ ADR)$$
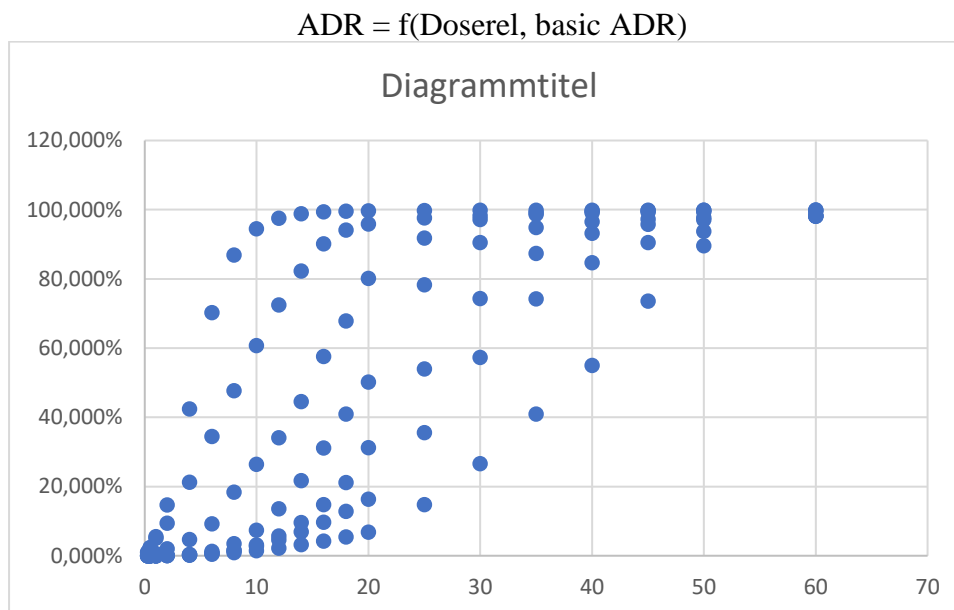
The aggregate value over all drugs and side effects in the **ADR CP** (Total ADR) may be higher than 100%; this Total ADR as well as the ADR/ Drug is useful when comparing different medication scenarios with the target to minimize the risk. Single ADRs shall accord to the Prescriber Information for a drug as approved by the FDA in the U.S. or the EMA in Europe or international scientific literature. Frequencies of side effects are most times assigned to classes which refer to the WHO probability classes of side effects: very common/frequent, common/frequent, occasional, rare, very rare (1).

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ADR Frequencies and Classes

Side effects may differ from each other by their severity. Taking regard of looking a) at dangerous/serious or b) important side effects ADR %-values are assigned to different ADR classes, see Table 1 and Table 2.

Table 1: a) ADR Frequencies and Classes for dangerous Side Effects (ADR-1)

ADR Frequency	ADR Class 1	Meaning in numbers	Reference number
0	0	means: 0	
Practically ZERO	No risk/light green	>= 0 and < 0,0005% means: 1 - 4 "the basic risk in the population ⇔ no risk"	Out of 1 million cases/persons
Extremely rare	Very low/light yellow	>= 0,0005% means: 5 - 10	Out of 1 million cases/persons
Very rare	Low/lightest red	>=0,001% means: 11 – 99	Out of 1 million cases/persons
Rare	Medium/light red	>=0,01% means: 100 – 999	Out of 1 million cases/persons
Occasional	High/orange-red/ or red	>=0,1% means: 1,000 – 9,999	Out of 1 million cases/persons
Frequent	Very high/red/ or red-black	>=1% means: 10,000 – 99,999	Out of 1 million cases/persons
Very frequent	Extremely High/black	>=10% means: more than 100,000	Out of 1 million cases/persons

Table 2: n) ADR Frequencies and Classes for important Side Effects (ADR-2)

ADR Frequency	ADR Class 2	Meaning in numbers	Reference number
0	0	means: 0	
Practically ZERO	No risk/light green	>= 0 and < 0,0005% means: 1 - 4 "the basic risk in the population ⇔ no risk"	Out of 1 million cases/persons
Extremely rare	Extremely low/green	>= 0,0005% means: 5 - 10	Out of 1 million cases/persons
Very rare	Very Low/light yellow	>=0,001% means: 11 – 99	Out of 1 million cases/persons
Rare	Low/yellow	>=0,01% means: 100 – 999	Out of 1 million cases/persons
Occasional	Medium/light orange	>=0,1% means: 1,000 – 9,999	Out of 1 million cases/persons

| Frequent | High/orange | >=1% means: 10,000 – 99,999 | Out of 1 million cases/persons |
| Very frequent | Very High/red | >=10% means: more than 100,000 | Out of 1 million cases/persons |

Higher ADR values are represented by bigger traffic lights than smaller ADR values and by red-black color or orange-black color in the **ADR CP.**

If several drugs in a medication cause the same side effect it is usually assumed that the cumulative effect and the ADR respectively are by a pharmacodynamic drug interaction increased. In particular the literature concerning the QT interval prolongation emphasizes this point (10, 11, 12, 13); this view is in accordance with the established drug policy to declare drug combinations contraindicated, not recommended or usable only with caution, dependent on the magnitude of the proven or potential risk. In the case that the blood concentration of a QT drug is substantially elevated through one or more other drugs (so called pharmacokinetic interaction), a dose dependent risk increase is assumed, in particular if the expected extent of the plasma level rise accords to overdosage (10, 11, 12). In the case that side effects of drugs may favor the precipitation of serious QT prolongations such as hypokalemia, hypomagnesemia, bradycardia, or heart failure (10, 11, 12, 13) additional risk scores may be taken into account following the method of Tisdale (12).

ADR and cumulative Risks

For purposes of assessing cumulative risks mean representative %-values of the ranges of these classes are used such as 20% (very frequent), 5% (frequent), 0.5% (occasional), 0.05% (rare), 0.005% (very rare), as more specific data is frequently not reported. If drug A has a 5%-frequency and drug B has a 5%-frequency of the side effect, the cumulative risk is 10% . Such a cumulative ADR is not necessarily the real side effect risk when drug A and B are used concomitantly, but it represents a rough indicator to judge this risk. Potential synergy effects and their consequences, therefore, have for now to be assumed by the user her- or himself. With higher doses of the drug(s) involved or high MDDI alert level, which signalize overdosing, a relatively higher ADR is assumed as the majority of side effects are represented by type A („augmented") dose-related effects (14) and nowadays even uncommon type B („bizarre") immune-mediated effects are increasingly regarded to be to some extent dose-related (15).

The basic formula for a specific ADR_i dependent on the side effect frequencies FREQ_ij and the AUCrel_j due to drug or multiple drug drug interactions of DRUGS_j (with i = 1….n side effects and j = 1….m drugs) is:

$$ADR\_ij = SUM (FREQ\_ij * f(AUCrel\_j))$$

Whereby applies in the default case a slightly overproportional ADR/FREQ increase according to the following rule of thumb:

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$$f(AUCrel) = AUCrel^2 /SQRT(AUCrel)$$

Risk factors may increase ADRs as multiplyers; such risk factors may exist for example due to age (RAGE), Sex (RSEX), renal stage or GFR (RREN), or pharmacogenetic properties (RPG) as well as risk favoring other side effects (RADR) and a risk potentiation factor RPF to mirror synergy effects. ADR CP Version 1.0 is confined to drug data; therefore only RADR may play a role, for example if drug related hypokalemia favors the occurrence of QT prolongation. Future ADR CP versions with an EMR interface will also process patient individual data.

Please note:

The SCHOLZ Databank ADR Software is according to the FDA policy NOT a Medical Device (16, 17). It enables the health care professional as a user to independently review the basis of the information provided by the specific ADR CP software functions, such that the health care professional does not rely primarily on the information to make a clinical decision about an individual patient; the user of the ADR CP is asked – and this is mandatory - to control any information provided through the ADR CP by her or his professional expertise and checking the up-to-date prescriber information and literature also available through the software. Any use of the ADR CP presumes the acceptance of the End User License agreement by the user.

MDDI: Assessing at one glance how one drug might be affected by ALL other drugs of the medication

MDDI: The new View on Drug Drug Interactions

The **MDDI** drug interaction technology supports a completely new view on drug drug interactions; Niemi et al. reported in 2000 and 2006 the results of two in-vivo-studies where repaglinide and loperamide respectively and their AUC were affected to an unexpectedly high extent through multiple drug drug interactions (2, 3) . Based on these findings and contributions from Ohno et al. (3) and Isoherranen et al. (4) a general concept for processing multiple drug drug interactions **(MDDI)** including especially drug absorption and metabolism was developed and incorporated into the SCHOLZ Databank drug interaction software which has been developed since 1980 (6, 7). **The MDDI** tool was helpful to better understand a published case report of rhabdomyolysis caused by the multiple impact of amlodipine and ciprofloxacin on the kinetics of simvastatin (8, 9). Thus it helps the user to recognize immediately, how one drug is kinetically affected by ALL other drugs of the medication. The **MDDI** alerts bring this message to the user; they symbolize the interaction magnitude by different colours from light yellow over red to black according to the relative increased AUC (AUCrel) of the drug affected by the interaction or multiple interactions.

Classical Drug Drug Interactions are usually presented through pairs of interacting drugs. In particular in polypharmacy it occurs frequently, however, that an adverse effect is subject to multiple pharmacodynamic
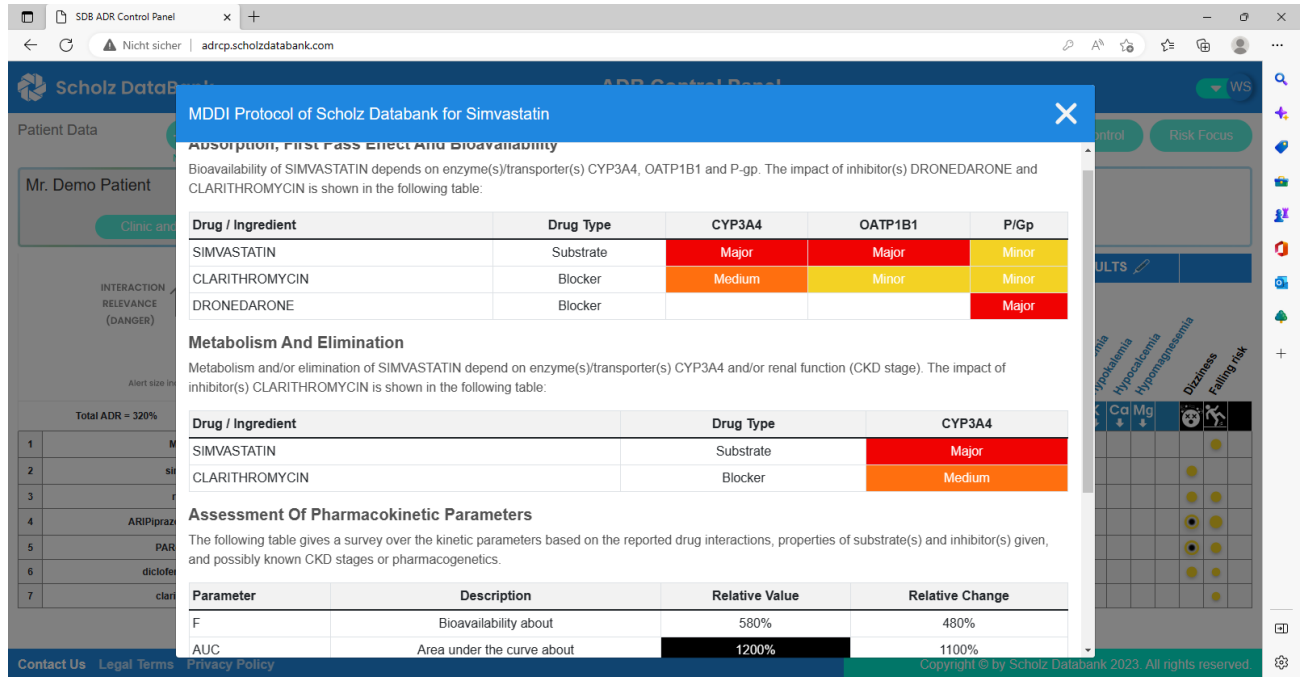
and/or pharmacokinetic impacts. Then it can become very tedious to puzzle together what might be the outcome when several drugs of a polymedication interact and have a direct or indirect impact on such an adverse effect. The MDDI technology overcomes this problem and makes possible to assess at one glance how one drug might be affected by ALL the other drugs of the medication. Let us look again at the already mentioned fictitious case of the multimorbide patient Willy Nottingham and his ADR CP in screen 12:

Screen 12:
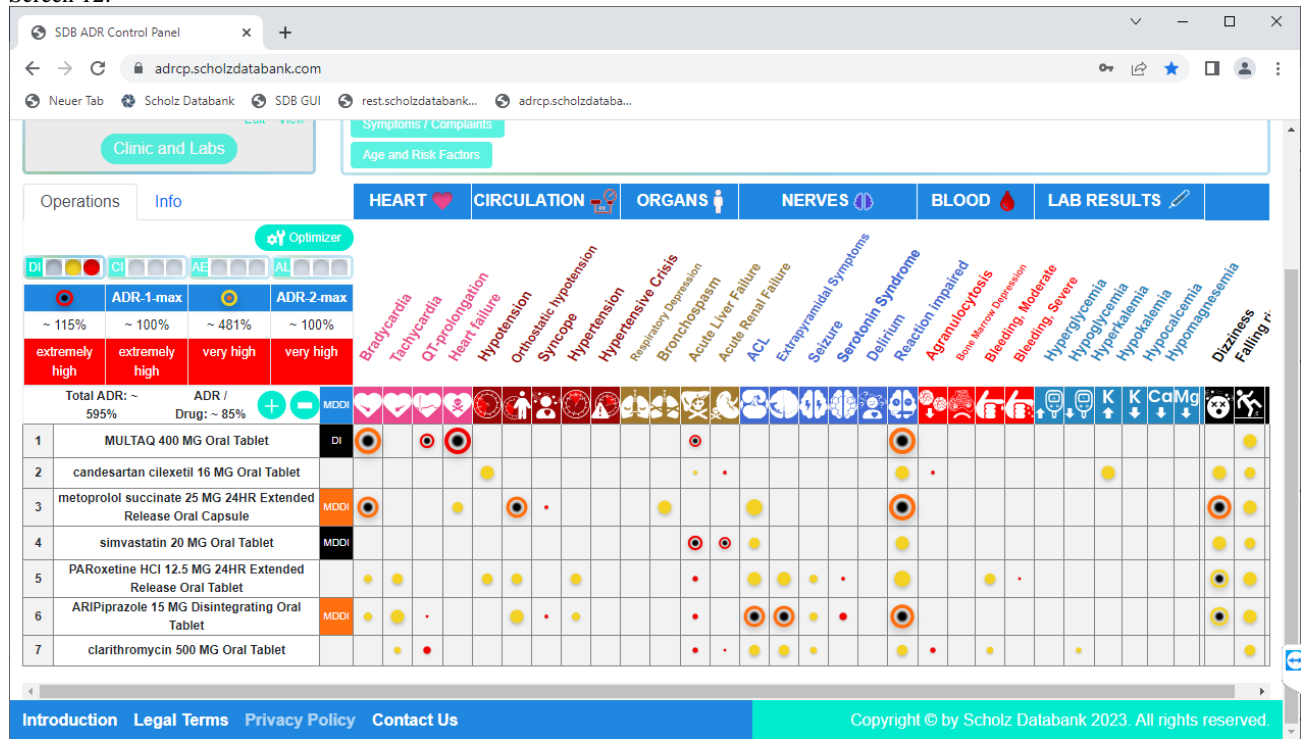
As visible through the MDDI buttons there is for example a major problem for simvastatin. The exposure to simvastatin amounts probably due to diverse inhibitions of transporters and enzymes to more than the 10-fold, which is unacceptable high. The following screen 13 of the MDDI protocol illustrates the scenario:

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Screen 13:

MDDI Protocol of Scholz Databank for Simvastatin

Absorption, First Pass Effect And Bioavailability

Bioavailability of SIMVASTATIN depends on enzyme(s)/transporter(s) CYP3A4, OATP1B1 and P-gp. The impact of inhibitor(s) DRONEDARONE and CLARITHROMYCIN is shown in the following table:

Drug / Ingredient	Drug Type	CYP3A4	OATP1B1	P/Gp
SIMVASTATIN	Substrate	Major	Major	Minor
CLARITHROMYCIN	Blocker	Medium	Minor	Minor
DRONEDARONE	Blocker			Major

Metabolism And Elimination

Metabolism and/or elimination of SIMVASTATIN depend on enzyme(s)/transporter(s) CYP3A4 and/or renal function (CKD stage). The impact of inhibitor(s) CLARITHROMYCIN is shown in the following table:

Drug / Ingredient	Drug Type	CYP3A4
SIMVASTATIN	Substrate	Major
CLARITHROMYCIN	Blocker	Medium

Assessment Of Pharmacokinetic Parameters

The following table gives a survey over the kinetic parameters based on the reported drug interactions, properties of substrate(s) and inhibitor(s) given, and possibly known CKD stages or pharmacogenetics.

Parameter	Description	Relative Value	Relative Change
F	Bioavailability about	580%	480%
AUC	Area under the curve about	1200%	1100%

The overview gives a transparent representation of substrates and blockers and which transporters and enzymes are involved and affected with the result that the exposure (AUC) of simvastatin is up to about 1200% meaning the 12-fold. More specific insights are available as Absorption and Metabolism chapters are separately shown, but the aggregate conclusion for the increased relative AUC is presented, too.

In scenarios where more than one comedications substantially influence the metabolism of the substrate at very different enzymes the MDDI technology helps the user in particular to keep the survey having much less hassle to puzzle together what the aggregate blocking effect out of these different impacts might be. Please remember the MDDI protocol of aripiprazole in screen 14.

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Screen 14:

MDDI Protocol of Scholz Databank for Aripiprazole

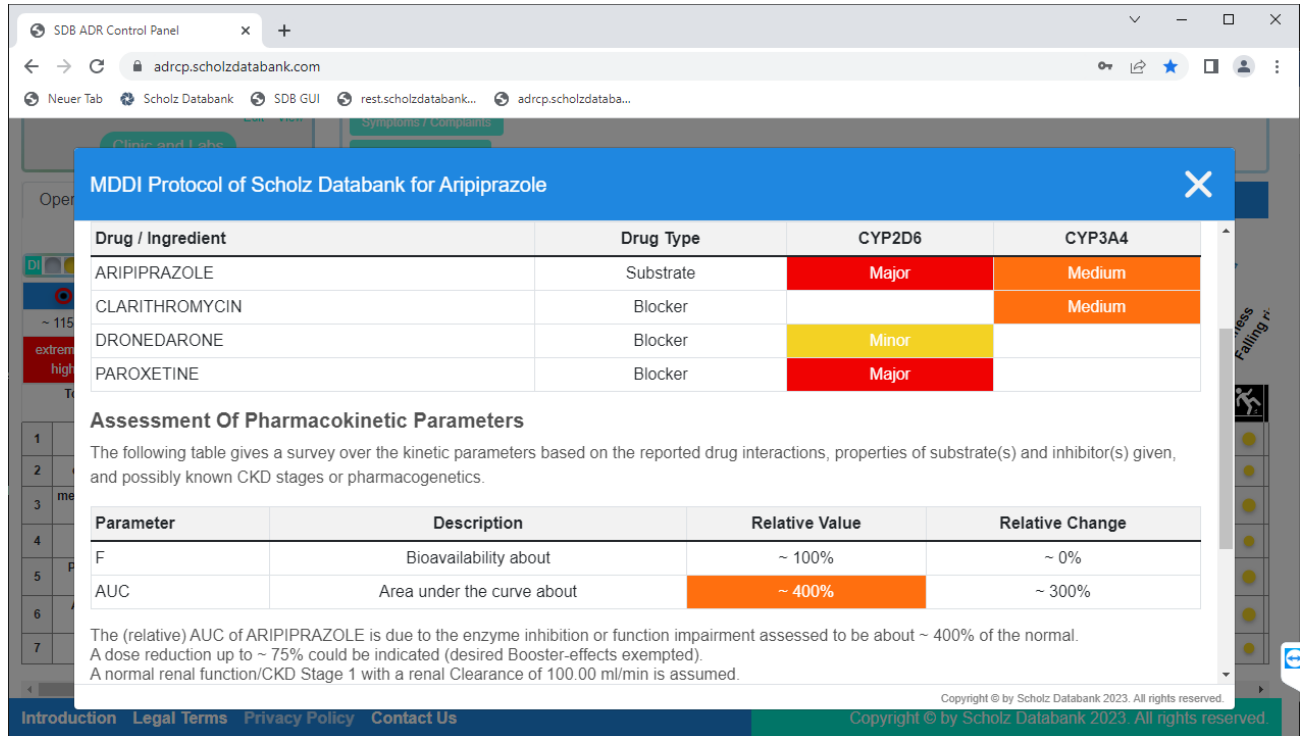| Drug / Ingredient	Drug Type	CYP2D6	CYP3A4
ARIPIPRAZOLE	Substrate	Major	Medium
CLARITHROMYCIN	Blocker		Medium
DRONEDARONE	Blocker	Minor	
PAROXETINE	Blocker	Major	

Assessment Of Pharmacokinetic Parameters

The following table gives a survey over the kinetic parameters based on the reported drug interactions, properties of substrate(s) and inhibitor(s) given, and possibly known CKD stages or pharmacogenetics.

Parameter	Description	Relative Value	Relative Change
F	Bioavailability about	~ 100%	~ 0%
AUC	Area under the curve about	~ 400%	~ 300%

The (relative) AUC of ARIPIPRAZOLE is due to the enzyme inhibition or function impairment assessed to be about ~ 400% of the normal.
A dose reduction up to ~ 75% could be indicated (desired Booster-effects exempted).
A normal renal function/CKD Stage 1 with a renal Clearance of 100.00 ml/min is assumed.

The concomitant inhibition of the aripiprazole metabolism through paroxetine/dronedarone at CYP2D6 and clarithromycin at CYP3A4 causes the increase of the AUC up to about 400% or the 4-fold, which is very well in line with what the Abilify prescriber information (18) tells in the chapters about pharmacokinetics and dosing, see the following Table 3:

Table 3: Dose Adjustments for ABILIFY

Dosage adjustment due to drug interactions:
Factors

                                      Dosage Adjustments for ABILIFY

Known CYP2D6 Poor Metabolizers
        Administer half of usual dose
Known CYP2D6 Poor Metabolizers and strong CYP3A4 inhibitors   Administer a quarter of usual dose
Strong CYP2D6 **o r** CYP3A4 inhibitors
        Administer half of usual dose
Strong CYP2D6 **and** CYP3A4 inhibitors
        Administer a quarter of usual dose

As the MDDI technology allows to taper very precisely the properties of the substrates and inhibitors involved, meaning how much a substrate is subject to one or more enzymes/transporters and how much enzymes or transporters might be blocked by an inhibitor, the MDDI assessments of the relative AUC changes accord very well to the results of in-vivo pharmacokinetic studies with deviations of less than 10% in most scenarios reported.

How the ADR CP may be interfaced to EMR and other Third Party Software

The ADR CP of SDB is available as a web-based application that can be used online as stand-alone software; SDB ADR CP can also be called through an interface from third party EMR or E-prescribing software and includes the option to submit coded patient data such as drug codes, ICD10-Codes and other patient individual information. Whereas this solution comes with a graphic UI the ADR CP can also be built as a web-based service with UI using the SDB web service based on REST Technology.

For technical details of interfacing please refer to the Appendix of this document: **Technical Description of the Interface to connect the ADR CP to EMR or E-prescribing software.**

References and Literature

SCHOLZ DataBank information is based on up-to-date international prescriber information, literature, and publications of Health Authorities such as the drug drug interaction guidelines of the FDA. Therefore the most recent Prescriber information according to the dailymed web service of the NIH can be retrieved for the drugs entered in the drug listing in the main screen of the **ADR CP** as well as literature related to drug drug interactions and MDDI including direct access to the Medline PUBMED literature service.

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Specific Literature for the ADR CP Introduction

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17) Policy for Device Software Functions and Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff Document issued on September 28, 2022. https://www.fda.gov/media/80958/download
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Appendix: Technical Description of the Interface to Connect the ADR CP to EMR or E-prescribing software

Introduction

The **SDBClientConnect** is a Cloud-based Software

SDBClientConnect will act as a middle layer between EMR and ADR CP software to transfer data.

The data will be transferred in the form of C-CDA (Consolidated Clinical Document Architecture). It's the most widely used format for health information exchange in the US today. Each patient encounter in the healthcare system can be represented by a single document in the Clinical Document Architecture (CDA) style.

SDBClientConnect will take data input from EMR and send it to ADR CP and provide the "all in one" overview of drug risks in a patient medication screen.

1. Functional Flow

2. 1.1. Showing the ADR CP screen

- Keep a centralized database of all EMR customers, their required information, and their assigned license key.

- The cloud EMR delivers the user's information (username, password, API key, and practice code) to **SDBClientConnect** via the POST method. **SDBClientConnect** verifies the user's information and creates a token with security encryption in accordance with OAuth 2.0 Specifications. The **SDBClientConnect** then returns the token if the user is legitimate.

- When the EMR receives the token from the **SDBClientConnect**, it returns the patient's medication details (in CCDA encrypted format) along with the generated token using the POST method.

- Gets the Drugcodes, based on RXCUI's code in Patient medication details

- Using the POST method, the **SDBClientConnect** sends the details (username, password, UCI, and timestamp) to ADRCP. ADRCP validates the details; if it is a valid request, the ADRCP then returns the ADRCPToken to **SDBClientConnect**.

- Using the POST method, **SDBClientConnect** sends the details (like drug codes and ADRCP tokens) to ADRCP and returns the URL to **SDBClientConnect**.

- The **SDBClientConnect** shows the ADRCP UI in an iframe using the given URL.

- The generated ADRCP UI output is sent back to **SDBClientConnect**

- **SDBClientConnect** shows the received ADRCP output in Iframe and returns to the EMR

3. 1.2. Getting info back from ADRCP screen

- The **SDBClientConnect** gets a request from EMR with the generated token using the GET method.

- When the **SDBClientConnect** receives the token from the **EMR**, it validates

- **Getting Started**
    1. To get started with ADRCP API, please follow these steps:
        i. Register with Scholzdatabank. please visit the following page to contact us
           https://scholzdatabank.com/contact-us
           you can also email us at
           management@scholzdatabank.com
        ii. After your registration, you will get a registered email & password. You can use these credentials to make a request to the ADRCP server.
        iii. Make requests to the appropriate endpoints using the HTTP methods. ADRCP follows the REST API approach.
- **SDBClientConnect** sends an E-mail, Password to ADRCP for Authentication using the **POST** method. The **SDBClientConnect** gets a generated ADRCP Token along with a redirect URL from ADRCP
    o 'POST /api/v1/users/login'
        ▪ Description: authenticate the user and create adrcp_token
        ▪ Parameters: email, password
        ▪ Response: 200 OK with a JSON object containing adrcp_token & a redirect_url.

```
▪   {
    "adrcp_token": "dVdaE87xoAEq1ybBXfDj",

▪    "email": "umair@gmail.com",
```

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```
    ▪      "redirect_url":                                    "https://adrcp.scholzdatabank.com/oauth",
           "redirect_url_with_adrcp_token":

           "https://adrcp.scholzdatabank.com/oauth?adrcp_token=dVdaE87xoAEq1ybBXfDj"

    ▪      }
```

- Please look in the response header for the response status code.
- Further communication should only be carried out through adrcp_token. Further communication through email and password is discouraged. redirect_url_with_adrcp_token can be used to log in.
- sample   URL
  https://adrcp.scholzdatabank.com/api/v1/users/login?email=useremail@gmail.com&password=user_password

- Using the POST method, **SDBClientConnect** sends the details (like drug codes and ADRCP tokens) to ADRCP and returns the URL to **SDBClientConnect**.
  - o 'POST /medicines/adr?medicine_ids='
    - Description: authenticate and add medicines to Medication 1.
    - Parameters: medicine_ids, adrcp_token
    - Response: 200 OK with a html document.
    - Please look in the response header for the response status code.
    - response is a proper HTML document that can be loaded in an iframe. This call also provides a user session and automatically switches user Medication to Medication 1 (that is the default user medication). any medicine added to Medication 1 is also added to Medication 2,3, and 4.
    - https://adrcp.scholzdatabank.com/medicines/adr?medicine_ids=Y13123,Y13944,Y23536,Y23723&adrcp_token=sPByYnxLrhw8gH9rp_wt
      (user your own adrcp_token here and medicine_ids are separated by comma)
    - This function provide two functionalities authentication and add medicines so only one call is needed to set up ADR CP in an iframe.
- **SDBClientConnect** sends ADRCPToken to ADRCP to get the patient's modified medication details to **SDBClientConnect** using **GET** method 'GET /api/v1/medicines/get_patient_drugs'
  - o Description: Get a list of drugs that the user added in ADRCP in the user current selected medication.
  - o Parameters: adrcp_token
  - o Response: 200 OK with a JSON array of drug objects.
 - o {
         "patdrugs": [
  - o   {

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```
o          "drug_name": "MULTAQ 400 MG Oral Tablet",

o           "rxcui": "854859",

o           "drug_code": "Y25289"

o        },

o        {

o           "drug_name": "simvastatin 80 MG Oral Tablet",

o           "rxcui": "200345",

o           "drug_code": "Y29173"

o        },

o        {

o           "drug_name": "clarithromycin 250 MG Oral Tablet",

o           "rxcui": "197516",

o           "drug_code": "Y17224"

o        }

o    ]

o    }
```

- o sample URL
  https://adrcp.scholzdatabank.com/api/v1/medicines/get_patient_drugs?adrcp_token=1rbh tb4rfq_6rxbdqhPH
  (please use your own adrcp_token here)
- o rxcui is only available for drugs that patient added using the ADRCP. it is not available for the drugs added to ADRCP using the API.
- **SDBClientConnect** converts the patient's medication details into CCDA format and sends it back to EMR

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4. 1.3. Flow diagram

➢ Calling ADRCP from EMR through **SDBClientConnect**
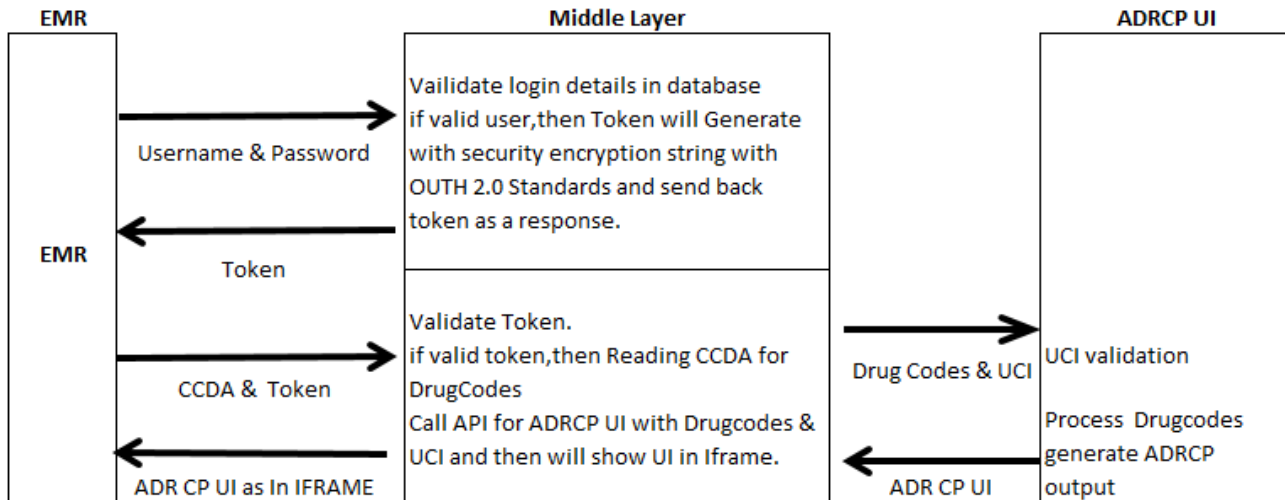
➢ Getting modified drugs info back from ADRCP to **SDBClientConnect**
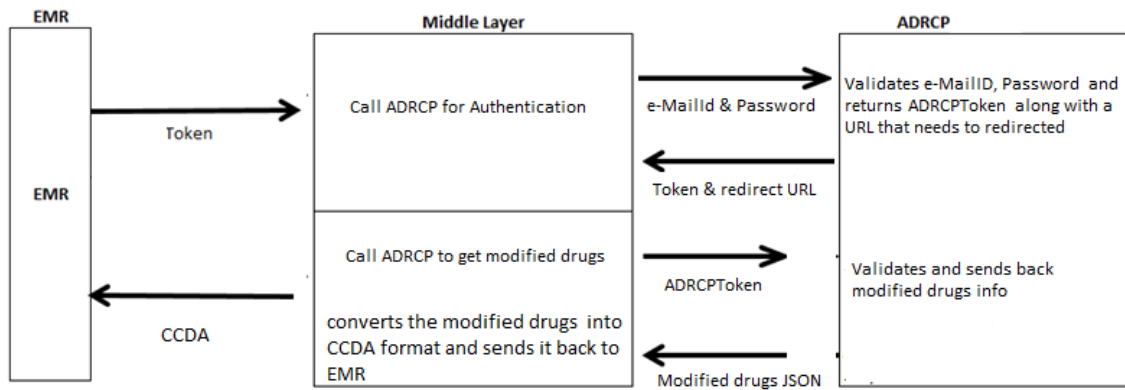
5. 1.4. Additional Screens in SDBClientConnect

- Admin Screens for EMR Client Management: (API Key's and Mapping Practice code & UCI management)

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6. Technical Flow

6.1 Database

1. **Customer** Table

    Add fields to (

        [UserName] [nvarchar](50) NULL,
        [Password] [nvarchar](50) NULL

2. **AuditLog**

    CREATE TABLE [dbo].[Audit_Log](

        [ID] [int] NULL,
        [CustomerID] [int] NULL,
        [AccessDate] [DateTime] NULL,
        [EMRData] [Text] NULL,
        [Response] [Text] NULL,
        [SessionID] [nvarchar](500) NULL

) ON [PRIMARY]

3. **Session** Table

    CREATE TABLE [dbo].[SDB_Session](

        [ID] [int] NULL,
        [CustomerID] [int] NULL,
        [SessionID] [Varchar](500) NULL,
        [AccessDate] [DateTime] NULL

) ON [PRIMARY]

6.2 SDBClientConnect Authentication API from EMR

API : http://localhost/api/auth/Authenticate

Type : POST call

Input : model

```
{
  "UserName":"ClientConnect",
  "Password":"Client1234",
  "APIKey":"DA-CONNECT-API-KEY-001",
  "Timestamp":"{{isoTimestamp}}"
}
```

Output : Token as String

6.3 Load ADRCP UI From EMR

API: http://localhost/Home/LoadADRCP
  Type: POST Call
  Input : model
  Header Key : Authorization(Token)
      { CCDA:"" (Base 64 encrypted string) }

  Output : ADRCP UI URL

6.4   **Get modified data from ADRCP to EMR through SDBClientConnect**
API: http://localhost/Home/GetADRCPModifiedDrugs
Type: GET Call
Input : model
Header Key : Authorization(Token)
Output : updated CCDA

6.5   **ADRCP Authentication from SDBClientConnect**
API : http://localhost/api/auth/ADRCPAuthenticate
  Type : POST call
  Input : model
      { "e-mailID":"e-mailID",
       "Password":"Client1234"}
  Output : ADRCPToken and Redirect-URL as String

6.6   **Data pullback from ADRCP to SDBClientConnect**

Call <Redirect-URL>
Type: GET Call
Input : model
Header Key : Authorization(ADRCPToken)
Output : Modified drugs in JSON format
The JSON will be converted into CCDA and send back as output to EMR for 2.4 "API:
http://localhost/Home/GetADRCPModifiedDrugs"

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