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Polypharmacy and Drug-Drug Interactions among Older and Younger Male Prisoners in Switzerland

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Abstract

Purpose: Our study determined the prevalence of polypharmacy and drug-drug interactions (DDIs) in older and younger prisoners, and compared if age group is associated with risks of polypharmacy and DDIs.

Methods: For 380 prisoners from Switzerland (190 were 49 years and younger; 190 were 50 years and older), data concerning their medication use were gathered. MediQ identified if interactions of two or more substances could lead to potentially adverse DDI. Data were analysed using descriptive statistics and generalized liner mixed models.

Results: On average, older prisoners took 3.8 medications, while younger prisoners took 2.1 medications. Number of medications taken on one reference day was higher by a factor of 2.4 for older prisoners when compared to younger prisoners ($p = .002$). The odds of polypharmacy was significantly higher for older than for younger prisoners (≥5 medications: Odds ratio = 5.52, $p = .035$). Age group analysis indicated that for potentially adverse DDI there was no significant difference (Odds ratio = 0.94; $p = 0.879$). However, when controlling for the number of medication, the risk of adverse DDI was higher in younger than older prisoners, but the result was not significant.

Originality/Value: Older prisoners are at a higher risk of polypharmacy but their risk for potentially adverse DDI is not significantly different from that of younger prisoners. Special clinical attention must be given to older prisoners who are at risk for polypharmacy. Careful medication management is also important for younger prisoners who are at risk of very complex drug therapies.

Key words: polypharmacy, polymedication, drug-drug interactions, prison, older prisoners

Introduction

Polypharmacy or polymedication literally means the use of more than one drug at any time. In the literature, it frequently denotes the concurrent use of five or more drugs (Jokanovic et al., 2015; Masnoon et al., 2017; Mosshammer et al., 2016; WHO 2018). Polypharmacy is sometimes also negatively connoted as the inappropriate use of multiple medications or as the use of medications that are not clinically indicated (Fulton and Allen 2005; Jokanovic et al., 2015). To date, there is neither an agreed-upon definition of polypharmacy nor a cut-off point regarding the number of medications involved (Masnoon et al., 2017). However, it is accepted that there are certain risks associated with polypharmacy. For instance, polypharmacy increases the risk for adverse drug reactions and decreases drug compliance (Hajjar et al., 2007; Shah and Hajjar 2012). In the elderly population, it is associated with inappropriate prescribing, functional decline, and an increased risk for geriatric syndromes (Hajjar et al., 2007; Maher et al., 2014; Shah and Hajjar 2012). Polypharmacy also increases the risk of drug-drug interactions (DDIs) (Hajjar et al., 2007; Maher et al., 2014). A DDI is a situation in which one drug modifies the effect of another when both are taken together (Marengoni and Onder 2015) and adverse DDI can increase toxicity or reduce effectiveness of the substances (Preston 2016). A *potentially* adverse DDI is one that can be predicted from the known pharmacological properties of the substances involved. The clinical outcome of each DDI depends on individual risk factors such as age, genetic disposition, current conditions, and treatment factors like dosage or duration of the therapy. Thus, only a small number of potentially adverse DDIs lead to clinically significant adverse drug reactions (Horn and Hansten 2011; Seymour and Routledge 1998). That is, not all potentially adverse DDIs are harmful. Moreover, the administration of drugs known to interact adversely is sometimes necessary and is an advisable practice under strict monitoring and when appropriate precautions are taken (Preston 2016). To decide whether a potentially adverse DDI is of clinical significance, it is necessary to examine each case individually,

considering additional factors like medical history, patient age, or current biomarkers (e.g. laboratory values or electrocardiogram recordings) (Preston 2016; van Roon et al., 2005).

DDIs are an important issue when caring for older and frail patients because of their greater disease burden and consequently disproportionate use of medications (Prince et al., 2015). Older patients' greater intake of medications is a concern in light of physiological changes such as decreased renal and liver functions, which at the same time increases the risk for adverse drug reactions (Ballentine 2008; Fulton and Allen 2005). It is estimated that DDIs are responsible for 4.8% of all hospital emergency department visits (Becker et al., 2007), and that appropriate prescribing has the potential to consequently reduce emergency department visits, hospital visits, and mortality (Gillespie et al., 2009; Spinewine et al., 2007).

Compared to older adults in the community, the prevalence of (multi-)morbidity is even higher among older prisoners (Binswanger et al., 2009; Fazel et al., 2001). Studies report that older prisoners live with more illness than younger ones (Fazel et al., 2001; Fazel and Baillargeon 2011; Wangmo et al., 2015; Watson 2016). Prisoners are often defined as "old" from 50 years of age due to accelerated aging (Loeb and AbuDagga 2006; Loeb et al., 2008). Today, older prisoners, aged 50 and more, are still a minority in the Swiss prison population (Moschetti et al., 2015) as well as prison population in other countries. However, they form one of the fastest growing prison sub-groups (Human Rights Watch 2012). The illness epidemiology of older prisoners coupled with their rising number hold increasing public health importance (Fazel and Baillargeon 2011), nationally and internationally.

There are numerous studies investigating polypharmacy among older people in general (Fulton and Allen 2005; Jokanovic et al., 2015; Maher et al., 2014; Shah and Hajjar 2012), studies examining the health of prisoners (Binswanger et al., 2009; Pfortmueller et al., 2013), and of older prisoners in particular (Fazel et al., 2004; Loeb and AbuDagga 2006; Loeb et al., 2008; Wangmo et al., 2015). Only a few studies have explored the drug prescribing practices for prisoners of all ages (Elger et al., 2002; Elger et al., 2004; Griffiths et al., 2012) and very

few have specifically examined the medication use among *older* prisoners (Fazel et al., 2004; Williams et al., 2010).

To our knowledge, polypharmacy and DDIs among prisoners have hardly been studied and neither has any study compared whether age group is associated with polypharmacy and drug interactions among this population. Therefore, the present study aims to fill this research gap by addressing four questions: (a) What are the prevalence of polypharmacy and DDIs among older and younger prisoners in Switzerland? (b) Are there age group difference in the prevalence of polypharmacy and DDIs? (c) Which medications (active pharmaceutical ingredients) are primarily involved in potentially adverse DDIs? (d) What is the prevalence of actual clinically significant adverse drug reactions among older and younger prisoners? This study provides epidemiological data to improve medication safety and consequently, the quality of medical care provided to older and younger prisoners in Switzerland and comparable countries.

Methods

Sample and data collection

This study is part of a larger project entitled "Agequake in Prisons". The aim of the project was to understand the overall health and healthcare circumstances of aging prisoners in Switzerland. It considers not only prisoners' medication use, but also a multitude of other health related factors such as disease burden and healthcare utilization (Wangmo et al., 2015; Wangmo et al., 2016). Fifteen prisons with a capacity of 2,198 places (76.4%) out of a total of 26 prisons fulfilling the study's inclusion criteria (long-term imprisonments, >20 places, housing prisoners aged ≥50, from German and French speaking cantons of Switzerland) agreed to participate in the study (see (Wangmo et al., 2015) for in-depth information). Eleven prisons declined participation due to lack of time and other resources. Ethics committees of all involved cantons approved the study.

Medical records of all prisoners, aged 50 and older, were collected from the participating prisons except for one, for which half of the sample of older prisoners' data were collected. From each prison, the same number of medical records belonging to younger prisoners (<50 years) was randomly collected to have a basis for comparisons between younger and older prisoners (see (Wangmo et al., 2015) for more information). Two research assistants visited the prisons between November 2011 and April 2014 and gathered data from the medical records. Concerning medication use, they extracted information on the medication names, type of prescription, start and stop of prescription, and status of medication at the day of data recording, e.g. active or not active. Medication names were entered along with their corresponding Anatomical Therapeutic Chemical Classification System (ATC) codes (www.whocc.no/atc_ddd_index/). The data entered were checked by independent assistants for consistency.

Twenty six medical records of female prisoners from two prisons were excluded because they cannot be treated with male prisoners as a homogenous group (Watson 2016) and their number was too small to carry out representative separate analyses. These two prisons are the only ones that incarcerate female prisoners with long-term sentences (please refer to Handtke and colleagues (2015) for information). Therefore, in this study, data of 380 male prisoners from 13 prisons were used and analysed.

Operationalisation of variables

Polypharmacy was measured by the number of medications taken by the individual prisoner on *one single reference day* (i.e. seven days before data assessment). It was defined as the concurrent use of two (polypharmacy in the 'literal' sense) or five (polypharmacy as often defined in the literature) or more medications.

Medications were drugs approved by the Swiss Agency for Therapeutic Products. Medications contain one or more active pharmaceutical ingredient(s). If a prisoner had the same prescription twice on the reference day, although in different "strength" (e.g. Olfen-

100® and Olfen-50®), those were counted as one medication (e.g. Olfen-150). A number of topical preparations like ointments that have no systemic effect and thus, not known to induce interactions were counted in the number of medications (polypharmacy) but excluded from the DDI analyses. For practical reasons, all vitamins and minerals sometimes containing a multitude of different active pharmaceutical ingredients were also excluded from the DDI analysis (but included in the medication count).

In this paper, the term potentially adverse DDI is used to refer to a possibly harmful adverse interaction of pairs of two active pharmaceutical ingredients, as identified by the clinical decision support software MediQ (https://www.mediq.ch) with moderate (level 3) or severe risk (level 4). If that interaction is, according to the estimation of two experienced clinical pharmacists (ML and RH), likely to cause clinically relevant adverse drug reactions, we refer to it as "A" - *clinically relevant DDI*. Here, we distinguish further between clinically relevant DDIs that are "A1" - caused by a *presumed prescription error* or "A2" - state of the art for the specific patient since there is *no better solution available*. In contrast, if that level 3 or 4 interaction is, according to the expertise of the pharmacists, not of clinical relevance for the patient, we refer it as "B" - *DDI not of clinical relevance*. Here, we differentiate between *state of the art prescriptions* ("B1") and clinically not relevant combinations, nevertheless likely to be unintended and the result of inattentiveness ("B2" - *harmless prescription error* probably without clinical relevance). If a drug combination requires constant monitoring of the patient, but relevant information is lacking in the available data from the prisoner's file, we refer to "C"- *monitoring needed but information lacking*.

Data management

Our study is based on medications that were administered to and taken by the prisoner on the reference day, including *firm prescriptions*, *vaccinations*, and *medications handed out* to the patient upon request. Excluded from all analyses were provisional prescriptions (i.e. *pro*

re nata medications) if it was not known whether those were administered on the reference day, and medications for which the type of prescription (firm or *pro re nata*) was not clear.

Ideally, the medical records contained information on the medication names, type of prescription, start and stop of each prescription, and status of medication on the day of data recording[1]. However, if the *start* date was not available, the medication was dropped from the analysis. When the start date was available but the stop date was not available, and the medication was recorded as status "active", stop date was considered equal to date of data recording. If the status was "unknown", the stop date was considered equal to start date and the medication as taken on this one day. If the start date was available but the stop date was not, and the medication was recorded as status "not active", "taken once" or "regularly" the day of data recording in the prison, the stop date was considered equal to the start date and the medication as taken on this day.

Data analyses

After data cleaning, all medications that were identified as active on the reference day were imported to MediQ software using a self-developed script/code file written in R (version 3.2.3) that extracted information about all pairwise drug-drug (active ingredients) interactions. MediQ was selected because it allows a comparison of an unlimited number of medications simultaneously. MediQ compares two active pharmaceutical ingredients (instead of drugs or drug-classes) at a time and its algorithms are primarily based on information related to the substances. Furthermore, important aspects like dosage or route of administration are provided as free text information for each interaction identified by the algorithms. MediQ differentiates between four interaction levels: highly relevant interaction, often contra-indicated (level 4, red); potentially clinical relevant interaction, monitoring warranted (level 3, orange); low interaction potential, only relevant in especially vulnerable cases (level 2,

[1] In one prison (XIII), type of prescription and stop date was available from the medical records only for very few medications. Not to lose an important amount of information, we added a presumed type of prescription and stop dates based on general prescription advices for certain drug classes (e.g. antidepressants).

yellow); and no indication for an interaction (level 1, grey) (cf. www.mediq.ch). We focused on level 4 and 3 interactions in our DDI analysis, leaving out the minor ones, as it has been shown that risk ratings with more than three levels can be confusing and the restriction of analysis to severe and moderate DDIs is associated with a rise in sensitivity and positive predictive power (Vonbach et al., 2008).

Consequently, two pharmacists individually examined all combinations of active pharmaceutical ingredients identified as *potentially harmful adverse interactions (levels 3 and 4)* and classified the interactions according to their actual clinical relevance into the categories explained above. A final classification of each individual drug combination for a patient was decided upon mutual agreement between the pharmacists and one of the first authors (BA).

We analysed the data using descriptive statistics and generalized liner mixed models (GLMM) (Agresti 2003) to examine if there was a difference between older and younger prisoners experiencing polypharmacy and potentially adverse DDI, with age group as fixed effect and prison as random intercept. The outcome of the first model (number of medications) indicated whether there was a difference between younger and older prisoners in the number of medications taken. In all remaining models, outcomes were dichotomous assessing whether polypharmacy or potentially adverse DDI according to the respective definition differed by age group. Data analysis was carried out using IBM SPSS Statistics 22.

Results

The final dataset comprised 190 younger (20 - 49 years) and 190 older (50 - 75 years) male prisoners with mean ages of 34.3 (SD 7.4) and 58.8 (SD 5.8) years, respectively. Mean time served in prison at day of data recording was 2.5 (SD 2.5) years for younger and 5.2 (SD 6.3) years for older prisoners.

Polypharmacy among younger and older male prisoners

Younger male prisoners (n=190) took a total of 156 medications on one reference day, comprising firm prescriptions, vaccinations, and other medications handed out to them. A

majority (60%) of them took no medications on the reference day, while 20.5% took one, 10% two, and 9.5% three or more medications (Table 1). Concerned by polypharmacy (≥2 medications) were roughly one in five younger prisoners (19.5%), while only 3.2% had polypharmacy of five or more medications.

Older prisoners (n=190) took a total of 409 medications on one reference day. In the older age group, 43.2% had taken no medication on the reference day, 16.3% have taken one, 12.1% two, and 28.4% three or more medications (Table 1). Polypharmacy (≥2 medications) was observed in 40.5% of older prisoners, while 14.7% were taking five or more medications.

Table 2 presents findings from the GLMM. The number of medications taken on one reference day was higher by a factor of 2.4 for older prisoners when compared to younger prisoners (Risk ratio = 2.36; p = .002). Similarly, the odds for polypharmacy was significantly higher for older than for younger prisoners (≥2 medications on reference day: Odds ratio = 3.01, p = .002; ≥5 medications on reference day: Odds ratio = 5.52, p = .035).

Potentially adverse DDIs among younger and older male prisoners

Among younger prisoners, a total of 251 combinations of active pharmaceutical ingredients[2] were tested for interactions using MediQ software. As shown in *Table 3*, only 25 combinations (10.0%) had a moderate potential (level 3, orange), and there was no indication of a severe (level 4, red) risk for adverse DDI. This means that among all younger prisoners with at least two medications on the reference day (n=37), 14 individuals (37.8%) were affected by at least one potentially adverse drug-drug combination level 3, moderate alert.

Among older prisoners, a total of 1,383 combinations of active pharmaceutical ingredients were tested for interactions of which only 70 combinations (5.1%) had a moderate interaction (level 3, orange), and one combination (0.1%) presented a severe (level 4, red) risk for potentially adverse DDI. Looking at all older prisoners with at least two medications on

[2]The number of combinations of active pharmaceutical ingredients differs from the number of drug combinations as some drugs contain multiple active pharmaceutical ingredients. Thus, in some cases (n=10) level 1 interactions (i.e. “no potential for interaction”) are produced in individuals with one medication, only.

the reference day (n=77), 28 (36.4%) were concerned by at least one potentially adverse drug-drug combination (level 3 moderate). One prisoner (1.3%) had a level 4 alert.

Age group analysis (see Table 2) for potentially adverse DDIs indicated that there was no age group difference between older and younger prisoners (Odds ratio = 0.94; p = 0.879). However, when we adjusted the model for number of medications taken in light of the fact that older prisoners took more medications than younger prisoners, the results slightly changed (Odds ratio = 0.34; p=0.07, i.e. older prisoners at lower risk than younger prisoners).

Medication combinations causing potentially adverse DDIs

In total, 95 combinations for 42 individuals depicted potentially adverse DDIs of moderate risk (level 3, orange). One combination in an older individual, led to a high risk alert (level 4, red). However, the pharmacists deemed this latter combination as not clinically relevant after detailed analysis. Thus, this combination was neglected for the following analyses. *Table 4* provides a list of all active pharmaceutical ingredients and the corresponding medications that resulted in potentially adverse DDIs as well as the risk ratios (RR). The RR is the number of individuals concerned by potentially adverse DDI caused by a certain active pharmaceutical ingredient in relation to the total number of individuals with this prescription. Pharmaceutical ingredient with the highest RR for potentially adverse DDIs was escitalopram (which interacted with tizanidine, omeprazole, topiramate, and quetiapine).

In younger prisoners, the substance resulting most often in potentially adverse DDIs is methadone (interacting with diazepame, zolpidem, tizanidin, quetiapine, lorazepame, zuclopenthixole, propranolol or midazolame), while in older prisoners, the substance in adverse DDIs is ASS (interacting with ibuprofen, diclofenac, clopidogrel, budesonide, naproxene, phenprocoumon or heparine).

Clinically relevant adverse drug reactions

In younger prisoners, according to the evaluation of our two clinical pharmacists, of the 25 drug combinations which were identified as potentially adverse DDIs (level 3, orange

alert), eight combinations (32.0%) were classified as clinically relevant "A" (*Table 5*, second column; also see Table 3). Additionally, one combination (4.0%) was classified by the pharmacists as clinically not relevant "B" for the individual patient, while they found that the prescription of another 16 drug-drug combinations (64.0%) would require monitoring of the patient "C" but information about such practice was not available from the medical records, which made a final judgement of the individual cases impossible.

In older prisoners, the pharmacists classified 11 combinations (15.7%) out of a total of 70 potentially adverse DDIs as clinically relevant "A" (*Table 5*, third column). A total of 20 combinations (28.6%) were classified as clinically irrelevant "B" in the individual patient, while the prescription of another 39 drug-drug combinations (55.7%) would require monitoring "C" but information about such practice was not available. Similar analyses were carried out using *individuals* as the basis instead of drug combinations (refer to Table 5).

Discussion

Polypharmacy and DDIs are serious medical concerns and studies evaluating them in the prison context are lacking. To our knowledge, this study is one of the very few to examine polypharmacy among prisoners and the first to explore potentially adverse DDIs among older and younger prisoners. Our results hence provide valuable and much needed data to understand medication prescription practices in prisons. It adds new information to the body of knowledge available on health and healthcare of older prisoners in Switzerland in particular and prisoners in general (Moschetti et al., 2015; Wangmo et al., 2015; Wangmo et al., 2016; Williams et al., 2010).

With regard to the research questions posed in this study, first, we find that one in two prisoners were administered at least one medication on the reference day. Among individuals who were administered at least one medication, the mean number of medications older prisoners took was 3.8 and younger prisoners, 2.1 medications. It is difficult to compare our results with studies carried out in the general population not only because of their inherent

differences but also because general population studies often present information on three time points, that is, before, during, and after hospitalization (Bucsa et al., 2013; Johnell and Klarin 2007; Vonbach et al., 2008). If we assume that our data represents before hospitalization information and disregard situational differences, then our findings could be deemed comparable. For instance, Bucşa and colleagues (2013) found a mean of four drugs taken at the same time by older patients before hospital admission, and Vonbach and colleagues (2008) also noted four drugs before hospitalization.

Nearly one in three prisoners in our sample was characterised as having polypharmacy defined as the use of two or more medications on a reference day. This proportion reduced to approximately one in ten when polypharmacy was defined more rigorously using five or more medications on the reference day. Furthermore, older prisoners faced polypharmacy (both definitions) more often than younger prisoners. The results remained significant for age group difference irrespective of how polypharmacy was defined. That older prisoners took significantly more medications than younger prisoners is an expected finding because of their higher disease burden (Fazel et al., 2001; Wangmo et al., 2015).

Second, from our potentially adverse DDI analysis, we find that only one prisoner had a severe interaction potential (i.e. MediQ level 4, red). Also, on one reference day, more than a third of the prisoners who had taken two or more medications were concerned by a potentially adverse DDI with a moderate interaction potential (i.e. MediQ level 3, orange alert). However, there was no statistically significant difference between older and younger prisoners, that is, both were at equal risk. At first sight, this is an unexpected finding, since it is known that polypharmacy is a significant medical concern, particularly for the older population (Ballentine 2008; Hajjar et al., 2007) and presence of polypharmacy is associated with risk of DDIs (Johnell and Klarin 2007; Seymour and Routledge 1998; Vonbach et al., 2008). Thus, one would expect older prisoners to have an elevated risk for potentially adverse DDI compared to younger prisoners simply because the risk increases with the number of

medications. When controlling for the number of medication taken, the risk of adverse DDI was higher in younger than older prisoners, though this result was short off being significant on the alpha=.05 level. The higher risk of younger prisoners for adverse DDI could be related to specific drug therapies that are required for a higher number of (former) drug users among younger prisoners.

Third, medications that caused potentially adverse DDI in our study sample were drugs with pharmaceutical ingredients such as escitalopram, diazepam, quetiapine, diclofenac, methadone, and ibuprofen. Similarly, other studies have reported that common medications like aspirin and medications belonging to the following groups: anticoagulants and NSAIDs (Johnell and Klarin 2007; Percha and Altman 2013) often result in adverse DDIs. In light of very few studies illustrating the use of medications by prisoners (Elger et al., 2002; Elger et al., 2004; Williams et al., 2010), it is advisable for prison physicians to know of possible DDIs when prescribing these common drugs in prisons and other drugs (listed in Table 4) that caused DDI risk in our study.

Finally, according to the individual rating of two pharmacists, considering individual cases (e.g. age, medical history) from the total sample, in 14 prisoners (3.7%) a clinically relevant adverse drug reaction was present (due to small numbers, it was not possible to statistically test for differences between age groups). Of the clinically relevant adverse drug reactions, nine were presumed prescription errors of clinical relevance, while the remaining was probably intentional. In certain situations, intentional DDIs are state of the art to prescribe a mixture of medications, which have tendencies to interact (Preston 2016; van Roon et al., 2005), and in these cases monitoring of the patient must be followed. In our study, we were unable to gather data on whether these patients with potential for adverse DDIs were under observation to ensure minimum harm or not. In their literature review, Griffiths and colleagues (2012) reported a lack of consistency between prescribers within a

facility and between different sites. They also noted that it can be problematic if prescribers work solely in correctional facilities since this may mean scarcity of unbiased information.

Study limitations

A key limitation of the study is that evaluation of polypharmacy and DDIs was not the main purpose of the overall project. This explains missing data as greater efforts were not put to ensure that all information could be obtained. This meant that we had to take certain decisions during data analysis to reach best data quality. Second, our results are based on data collected from the medical records of prisoners, thus, we cannot confidently state that the medications indicated as active on the reference day were effectively taken, but this is reasonable assumption. Related to the limitation above, we cannot control which other illegal substances (cannabis, heroin, cocaine – of which prevalence rates are high in prisons (see (Annaheim et al., 2018))) were taken in parallel to the prescribed drugs. We were not able to test for such interactions. Third, although it is stated that polypharmacy is more common in women than in men (e.g. (Fulton and Allen 2005)), our sample did not contain enough female prisoners (n=26) to allow a meaningful analysis on this sub-group. Fourth, MediQ identifies only two active substances at a time. The risks of multiple DDIs, hence, may be underestimated. Finally, the number of medications taken can be a conservative estimate since four prisons either did not provide or only provided limited access to information related to psychiatric care. Thus, there is risk of under-reporting of psychotropic medications included in our analysis.

Conclusion

To our knowledge, this is the first attempt at the national level to explore this topic. Although we were not able to improve the therapy for the individual patient as part of our study because of its retrospective nature, it provides data to better understand the specific care situations of older and younger prisoners and to improve medication safety when caring for

these groups. Older prisoners are at a higher risk for polypharmacy than younger prisoners but their risk for potentially adverse DDI is not significantly different from that of younger prisoners. Adequate medication practices in prisons require necessary considerations to specific sub-groups. This means paying special attention to older prisoners who are at risk for polypharmacy, on the one hand, and on younger prisoners who are at risk of very complex drug therapies (often involving opioid substitution treatments), on the other hand.

Compliance with Ethical Standards

Ethics approval and consent to participate: 10 cantonal ethics committees approved this study (EKBB Basel, Bern, Aargau, Luzern, St. Gallen, Valais, Vaud, Fribourg, Zurich and Thurgau); EK 184/11. Anonymous data was collected from medical records requiring no consent from data subjects.

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Competing interests: The authors declare that they have no competing interests.

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Table 1: Prevalence (%) of polypharmacy among younger (n=190) and older (n=190) prisoners when considering number of medications taken on one reference day

Number of medications per individual	Younger prisoners n (%)	Older prisoners n (%)	Total n (%)
0	114 (60.0)	82 (43.2)	196 (51.6)
1	39 (20.5)	31 (16.3)	70 (18.4)
2	19 (10.0)	23 (12.1)	42 (11.1)
3	10 (5.3)	14 (7.4)	24 (6.3)
4	2 (1.1)	12 (6.3)	14 (3.7)
5 or more	6 (3.2)	28 (14.7)	34 (8.9)
Mean (SD)[a]	2.1 (1.7)	3.8 (3.3)	3.1 (2.9)
Median, mode, maximum [a]	1, 1, 9	2.5, 1, 16	2, 1, 16

[a]Mean, median and mode are calculated based on all individuals with at least one medication on reference day: Young: n=76, Old: n=108.

Table 2: Differences between younger and older prisoners for number of medications taken, risk of polypharmacy, and potentially adverse drug-drug interactions (DDIs)

	B	*SE*	*t-value*	*Risk Ratio/ Odds ratio*[a]	*95% CI for Risk/Odds ratio*	*p-value*	*n*
Number of medications	0.860	0.281	3.05	2.36	1.35, 4.11	.002	380
Polypharmacy 2+ medications	1.104	0.348	3.17	3.01	1.52, 5.98	.002	380
Polypharmacy 5+ medications	1.709	0.807	2.12	5.52	1.13, 27.02	.035	380
Potentially adverse DDI[b]	-0.063	0.414	-0.10	0.94	0.42, 2.11	.879	114[d]
Potentially adverse DDI[c]	-1.076	0.594	-1.81	0.34	0.10, 1.10	.073	114[d]

B = Coefficient indicating the difference between the two age groups; SE = Standard Error of B; [a] Risk ratio denotes by which factor the number of medications is higher in older compared to younger prisoners. Odds ratio denotes by which factor the odds for polypharmacy is higher in older prisoners than in younger prisoners; [b] Not controlled for number of medications. We used a general linear model (GLM) rather than a GLMM due to fitting problems resulting from the fact that the estimated variance for the random intercept was redundant; [c] Controlling for number of medications; [d] Individuals with ≥ 2 medications on reference day.

Table 3: Potentially adverse drug-drug interactions among younger and older prisoners according to a clinical decision support software (MediQ)

	Basis: Total *combinations* of active pharmaceutical ingredients			**Basis: *Individuals* with ≥2 medications on reference day***		
Interaction potential (risk level)	**Younger (%) n=251**	**Older (%) n=1383**	**Total (%) n=1634**	**Younger (%) n=37**	**Older (%) n=77**	**Total (%) n=114**
none (1, grey)	155 (61.8)	867 (62.8)	1022 (62.6)	21 (56.8)	64 (83.1)	85 (74.6.3)
low (2, yellow)	71 (28.3)	445 (32.2)	516 (31.6)	26 (70.3)	61 (79.2)	87 (76.3)
moderate (3, orange)	25 (10.0)	70 (5.1)	95 (5.8)	14 (37.8)	28 (36.4)	42 (36.8)
severe (4, red)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	1 (1.3)	1 (0.9)

*The column numbers (n) do not add up to the total n (Younger, Older and Total) as some individuals have DDIs of different risk levels (e.g. an individual can have two level 3 and one level 2 alerts).

Table 4: Active pharmaceutical ingredients (in alphabetical order) most often involved in potentially adverse drug-drug interactions (DDI) of moderate risk (level 3, orange) in prisoners

Active pharmaceutical ingredient (medication/product names)	Individuals affected by DDI * N=380	Total with this prescription N=380	Risk ratio** (number of DDI / total with prescription)	Potentially adversely interacting with (active pharmaceutical ingredients)
Acetylsalicylic acid (Aspirin Cardio, Cardiax)	10 (2.6 %)	23 (6.1 %)	0.43	Budenosid, Clopidogrel, Diclofenac, Heparine, Ibuprofen, Naproxen, Phenprocoumon
Diazepam (Valium Roche, Paceum, Psychopax)	4 (1.1 %)	5 (1.3 %)	0.80	Esomeprazol, Methadone, Tizanidin, Zuclopenthixol
Diclofenac (Olfen, Cofec)	4 (1.1 %)	7 (1.8 %)	0.57	Acetylsalicylic acid, Candesartan, Ibuprofen, Lisinopril
Escitalopram (Cipralex, Citalopram Actavis)	4 (1.1 %)	4 (1.1 %)	1.00	Olanzapin, Omeprazol, Tizandin, Topiramat, Quetiapine
Ibuprofen (Irfen, Spedifen, Brufen)	7 (1.8 %)	13 (3.4 %)	0.54	Acetylsalicylic acid, Budenosid, Diclofenac, Enalapril, Flecainid, Irbesartan, Lisinopril, Naproxen, Valsartan, Venlafaxin
Lisinopril (Lisitril, Lisinopril, Prinil Mepha)	6 (1.6 %)	13 (3.4 %)	0.46	Diclofenac, Ibuprofen, Naproxen, Spironolacton
Methadone (Methadon)	6 (1.6 %)	11 (2.9 %)	0.55	Diazepam, Lorazepam, Midazolam, Propranolol, Quetiapine, Tizanidin, Tramadol, Zolpidem
Omeprazole (Esomep, Omeprazol, Nexium)	6 (1.6 %)	24 (6.3 %)	0.25	Clopidogrel, Diazepam, Escitalopram, Pantoprazol, Phenprocoumon
Quetiapine (Seroquel)	6 (1.6 %)	9 (2.4 %)	0.67	Amitryptilin, Escitalopram, Methadone, Mirtazapin, Risperidon, Valproat

*Listed are only those medications involved in potentially adverse DDI in more than three individuals.
**Note that numbers for most common prescriptions are rather low and, thus, calculated risk ratios might be influenced by chance.

Table 5: Clinical relevance of adverse drug interactions among younger and older prisoners according to individual ratings of two pharmacists

	Basis: Number of potentially adverse *drug combinations* (a)			**Basis: *Individuals* with at least one potentially adverse DDI** (b)		
	Younger (%) n=25	**Older (%) n=70**	**Total (%) n=95**	**Younger (%) n=14**	**Older (%) n=28**	**Total (%) n=42**
A. Clinically relevant	8 (32.0)	11 (15.7)	19 (20.0)	5 (35.7)	9 (32.1)	14 (33.3)
A1. presumed prescription error	4 (16.0)	8 (11.4)	12 (12.6)	3 (21.4)	6 (7.8)	9 (21.4)
A2. no better solution available	4 (16.0)	3 (4.3)	7 (7.4)	2 (14.3)	3 (3.9)	5 (11.9)
B. Clinically not relevant	1 (4.0)	20 (28.6)	21 (22.1)	0 (0.0)	5 (6.5)	5 (11.9)
B1. state of the art prescription	1 (4.0)	18 (25.7)	19 (20.0)	0 (0.0)	5 (6.5)	5 (11.9)
B2. harmless prescription error	0 (0.0)	2 (2.9)	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
C. Possibly clinically relevant	16 (64.0)	39 (55.7)	55 (57.9)	9 (64.3)	14 (18.2)	23 (54.8)

(a) counted are all drug combinations, i.e. multiple per individual
(b) counted is the most serious combination per individual (i.e. A1 > A2 > C > B2 >B1), only