International Journal of Clinical Medicine Research
2018; 5(1): 7-14
http://www.aascit.org/journal/ijcmr
ISSN: 2375-3838

AASCIT American Association for Science and Technology

Application of the GerontoNet ADR Risk Score in a Psychiatric Setting

Gudrun Hefner[1, *], Martina Hahn[2], Sibylle C. Roll[2], Ansgar Klimke[1], Christoph Hiemke[3]

[1]Psychiatric Hospital, Vitos Klinik Hochtaunus, Friedrichsdorf, Germany
[2]Psychiatric Hospital, Vitos Klinik Eichberg, Eltville, Germany
[3]Department of Psychiatry and Psychotherapy, University Medical Center of Mainz, Mainz, Germany

Email address

Gudrun.Hefner@vitos-rheingau.de (G. Hefner)

[*]Corresponding author

Citation

Gudrun Hefner, Martina Hahn, Sibylle C. Roll, Ansgar Klimke, Christoph Hiemke. Application of the GerontoNet ADR Risk Score in a Psychiatric Setting. *International Journal of Clinical Medicine Research.* Vol. 5, No. 1, 2018, pp. 7-14.

Received: January 28, 2018; **Accepted**: February 18, 2018; **Published**: March 10, 2018

Abstract: Preventing predictable adverse drug reactions (ADRs) in elderly patients is a key focus of actual pharmacotherapy. Approaches to improve safety of pharmacotherapy in the elderly have been developed, amongst others the GerontoNet ADR risk scale. We assessed the applicability of this scale in the psychiatric setting. Hospitalized patients ≥65 years for whom blood-level measurement of a psychotropic drug were requested were included in the study. The diagnostic accuracy of the score in predicting moderate to severe ADRs in these patients was evaluated by receiver operating characteristics (ROC) analysis. In total, 79 patients (65.8% female) with a mean age of 73.5±5.4 years could be included in the study. Patients received by mean 8.8±3.9 drugs. Mean GerontoNet ADR risk score was 3.7±2.3 (range 0-7). A threshold value between 4 and 5 was computed to identify patients who are at high risk for moderate to severe ADRs. For this value predictive validity exhibited 71% sensitivity and 84% specificity (AUC: 0.808, 0.708-0.908, 95% CI). The score seems to be a good predictor for psychiatric patients who are at increased risk for an ADR. However, this tool is mainly based on the number of drugs ingested by the patient and does not consider several further risk factors associated with ADRs, as too high drug serum concentrations. We suggest to replace some variables in the GerontoNet ADR risk score for the psychiatric setting.

Keywords: Therapeutic Drug Monitoring, Adverse Drug Reactions, Risk Score, Elderly Patients, Psychiatry

1. Introduction

The incidence rate of adverse drug reactions (ADRs) is increasing rapidly, and because of several reasons, aged patients have a disproportionately high percentage of ADRs, compared with younger patients [1]. Elderly patients are particularly sensitive for the development of ADRs, especially because of age-related pharmacokinetic and pharmacodynamic changes [2, 3] and a high prevalence rate of multimorbidity and polypharmacy [4, 5] which increases the risk of drug interactions [6]. Beijer and colleagues [7] revealed that for aged patients, the possibility of being hospitalized because of an ADR is four times higher than for younger ones (16.6% vs. 4.1%). They further analyzed that in the elderly, up to 88% of the ADR related hospitalizations are preventable, compared with 24% in younger people [7]. Preventing predictable ADRs in elderly patients is a key focus of future clinical medicine [8], and several approaches to improve safety of pharmacotherapy in the elderly have been developed [9]. Amongst others, different screening tools to identify those patients who are at high risk of an ADR [10, 11] have been developed, e.g. the GerontoNet ADR risk score [12]. For the development and validation of the GerontoNet ADR risk score, Onder and coworkers [12] analyzed in hospitalized patients ≥65 years variables associated with an ADR and assigned risk points to each variable. Variables included in the score were ≥4 comorbid conditions (1 point), heart failure (1 point), liver disease (1 point), number of drugs (5-7 drugs = 1 point; ≥8 drugs = 4 points), previous ADR (2 points) and renal failure (1 point). The most powerful predictor of an ADR was the use of 8 or more drugs [12], receiving the highest risk points of all

included variables in the score. The risk score was validated in elderly patients who were admitted to university hospitals. Indeed, the GerontoNet risk score had a satisfactory predictive value for ADRs in the validation study [12], but also incorrectly classified 38% of patients as low risk in a study by O'Connor and colleagues [13]. Especially in geriatric psychiatry, polypharmacy is frequent [14, 15] and multiple further risk factors do foster the risk of ADRs. Amongst others, psychotropic drugs are independent risk factors for ADRs [16, 17]. Furthermore, the GerontoNet ADR risk score [12] considers hepatic and renal disease as risk variables. However, in psychiatry, drug serum concentration could be a better objective indicator for the total drug-clearance [18] than diagnosis of hepatic and renal disease. Therefore, psychotropic drug serum concentrations above the therapeutic reference range or even above the alert-level may be a stronger indicator for the development of ADRs [18, 19]. Accordingly, risk factors that were listed in the GerontoNet ADR risk score [12] could differ in clinical strength and relevance when the score is applied in the non-validated psychiatric setting. Til date, no study analyzed the suitability of the GerontoNet risk score [12] in a psychiatric setting. We aimed to assess the clinical applicability of this score in the psychiatric setting. In addition, an association between too high drug serum concentrations and the occurrence of ADRs was examined [18].

2. Study Design and Methods

2.1. Patients

This retrospective analysis was conducted at the Department of Psychiatry and Psychotherapy, University Medical Center Mainz, Germany. Because of the retrospective nature of the study, real-life pharmacotherapy of elderly patients could be studied. Data were obtained from 117 hospitalized patients ≥65 years for whom blood-level measurements of a psychotropic drug were requested at the Neurochemical Laboratory of the Department of Psychiatry and Psychotherapy, University medical center, Mainz (April/2011 to October/2012). Patients were excluded from analysis when the evaluation of causality and type of ADR [20] was not possible, for example because of acute detoxification or moderate to severe dementia at the time of blood-withdrawal. Elderly patients who were non-adherent or who had no trough-level conditions at the time of blood-withdrawal [18] were also excluded. When multiple serum level measurements were requested for the same patient, only the last analysis was considered.

2.2. Data Collection and Clinical Assessment

TDM-request forms contained information on patients´ characteristics, medication and ADRs. Data from request forms were supplemented with information from medical files. The assessment of ADRs by the treating physician was made using the UKU (Udvalg for Kliniske Undersøgelser) side-effect rating-scale [20]. The severity of ADRs was graded by a 4-point-scale, ranging from 0 (no side-effects) to 3 (severe side-effects). The causality-assessment of an ADR was made by a 3-point scale (implausible, possible or plausible) [20]. Only plausible and possible ADRs were included in the study. In the case of incomplete information on the request form, a clinical pharmacist examined medical and nursing records for ADRs reported around the time of blood-withdrawal. In general, patient-characteristics like age, gender, diagnosis according to International classification of Mental and Behavioural Disorders, 10th Revision (ICD-10), comorbidities and medication were collected for analysis. The total number of ingested drugs per day was calculated. Topical, ophthalmic, inhaled, otologic medications, dietary supplements and medical devices were excluded from calculation. Furthermore, the number of potentially inappropriate drugs according to the Priscus List [21] has been checked. Number of comorbidities was quantified by summarizing all clinical diagnoses as mentioned in the medical file. Previous illnesses and surgeries were not considered for the calculation. Heart failure was defined as any clinical diagnosed heart disease, except status after myocardial infarction. Liver disease was defined as any clinical relevant illness of the liver. Onder et al. [12] defined renal disease as a glomerular filtration rate of less than 60 ml/min. In this study, measurement of GFR was retrospectively not possible. Renal disease was defined as diagnosis of any kidney disease. Finally, we assessed the GerontoNet ADR risk score by Onder and colleagues [12]. The GerontoNet ADR risk variable for patients taking five medications is inconsistent, as it is included twice as ≤5 (0 points) and 5-7 drugs (1 point) in the score [12]. Consequently, when patients took five drugs per day, we assigned one risk point to them.

2.3. Analysis of Serum Concentrations

Serum levels of psychotropic drugs have been measured by using an isocratic reversed-phase high performance liquid chromatography (HPLC)-method with ultraviolet or fluorescence detection. The methods were developed and validated in the Neurochemical Laboratory of the Department of Psychiatry and Psychotherapy, University medical center, Mainz and fulfilled the criteria of the GTFCh guidelines [22]. The therapeutic reference-ranges and the alert-levels for the psychotropic drugs were taken from the TDM consensus guidelines 2017 [18].

2.4. Statistical Analysis

Using Spearman´s correlation analysis and linear regression, a possible association between the calculated GerontoNet ADR risk score [12] and the severity of ADRs (UKU) was determined. Furthermore, calculated risk scores were plotted against the severity of ADRs (UKU). The diagnostic accuracy of the GerontoNet ADR risk score [12] in predicting moderate to severe ADRs was evaluated by receiver operating characteristics (ROC) analysis. In addition, a threshold value which has a good balance between sensitivity and specificity

was calculated by ROC analysis to identify elderly patients who are at high risk for ADRs. The chi-square ($\chi 2$) test for independence was used for comparisons between patients who had moderate to severe ADRs and those who had not and therefore to analyze significant associations between the occurrence of an ADR and too high drug serum concentrations [18]. Results were presented as odds ratios (OR) with 95% confidence intervals. Comparisons between groups were computed using One-way analysis of variance (ANOVA). Descriptive statistics included mean values plus/minus standard deviations (±SD) and minimum and maximum values (Min-Max) were specified. Statistical analysis was carried out using IBM® SPSS® Statistics version 21.0 (IBM GmbH, Ehningen, Germany). A p-value <0.05 was considered as statistically significant.

3. Results

In total, 79 patients (65.8% female) with a mean age of 73.5±5.4 years (range 65-84 years) could be included in the study. Mean duration of hospitalization was 49±28.7 days (Table 1). Most frequent diagnoses (ICD-10) were recurrent depressive disorder with a severe current episode without psychotic symptoms (F33.2) with 41.8% and a severe depressive episode without psychotic symptoms (F32.2), occurring in 12.7% of all patients. In addition, 8.9% of the patients had a major severe depressive disorder, recurrent, with psychotic symptoms (F 33.3). 7.6% of the patients developed a recurrent moderate major depressive disorder (F33.1). Patients received by mean 8.8±3.9 drugs (range 1-18), including, by mean, 0.94±0.82 potentially inappropriate drugs (range 0-3, Table 1) [21]. Potentially inadequate antidepressants and antipsychotics, as defined by the Priscus list, were taken in 15 cases (19.0%) [21]. Mean UKU severity-index of ADRs was 1.56±0.81 (0= no side-effects, 1= low side-effects, 2= moderate side-effects, 3= severe side-effects). Overall, 7 patients (8.8%) showed no, 30 patients (38.0%) low, 33 patients (41.8%) moderate and 9 patients (11.4%) severe ADRs (Table 1). Mean GerontoNet ADR risk points (Table 1, 2) were 3.7±2.3 (range 0-7, Table 1). Patient frequencies concerning the risk variables included in the ADR risk score were described in table 3. GerontoNet ADR risk points correlated significantly (Figure 1) with observed ADRs (R^2=0.252, p<0.001, CI 95%). Spearman correlation-coefficient was 0.525 (p<0.01, CI 95%). A threshold value between 4 and 5 was computed by ROC-analysis (Figure 2) to identify patients who are at high risk for moderate to severe ADRs. For this value, predictive validity exhibited 71% sensitivity and 84% specificity (AUC: 0.808, 0.708-0.908, 95% CI). 45.6% of the patients had attained 5 or more GerontoNet ADR risk points (Table 2). In total, 112 drug serum levels have been measured, of which 28 serum level measurements (25.0%) were requested for venlafaxine, 26 (23.2%) for mirtazapine, 11 (9.8%) for citalopram and 9 (8.0%) for risperidone. Quetiapine and nortriptyline serum level measurements were requested in 7 cases (6.25%) for each drug. By mean, 1.42±0.55 serum level measurements have been requested for each patient. 29.1% of the elderly developed serum levels above the therapeutic reference-range [18]. In two cases, serum levels were above the alert-level [18]. Patients with serum concentations above the therapeutic reference-range [18] had significantly (p<0.05) more ADRs, compared with people within the therapeutic reference-range (Table 3) [18]. There was a statistically significant association between too high serum levels of the drug (χ^2 = 7.66; p<0.01; OR: 4.27, 95% CI: 1.47-12.38) and the occurrence of ADRs.

Table 1. *Sample characteristics of elderly psychiatric inpatients (n=79) for whom TDM has been requested.*

		Patients (n; %)	Min-Max	Mean (±SD)
Number of patients		79 (100.0)	N/A	
Age [years]		N/A	65-84	73.5±5.4
Gender	Female	52 (65.8)	N/A	
	Male	27 (34.2)		
Duration of hospitalization [days]			4-151	49.4±28.7
Number of medication		N/A	1-18	8.8±3.9
Number of potentially inappropriate drugs [21]			0-3	0.9±0.8
Number of potentially inappropriate drugs [21]	0	26 (32.9)	N/A	
	1	35 (44.3)		
	2	15 (19.0)		
	3	3 (3.8)		
Severity of adverse drug reactions (UKU)	none	7 (8.8)		
	low	30 (38.0)		
	moderate	33 (41.8)		
	severe	9 (11.4)		
GerontoNet ADR risk points [12] [n]		N/A	0-7	3.7±2.3

[12] Onder et al.; 2010
[21] Holt et al.; 2010

Table 2. *Frequency of summarized GerontoNet ADR risk points of elderly psychiatric inpatients (n=79) for whom TDM has been requested.*

		Frequency [n, %]
Summarized GerontoNet ADR risk points [12]	0	7 (8,9)
	1	16 (20,3)
	2	6 (7,6)
	3	1 (1,3)
	4	13 (16,5)
	5	10 (12,7)
	6	21 (26,6)
	7	5 (6,3)
	Total	79 (100,0)

[12] Onder et al.; 2010

Table 3. *Frequencies of risk variables for the occurrence of ADRs, as mentioned in the GerontoNet ADR risk score, in elderly psychiatric inpatients (n=79) for whom TDM had been requested. In addition, frequencies of too high psychotropic drug serum-levels and potentially inappropriate medications, as defined by the Priscus list, were described. Frequencies of no to low and moderate to severe ADRs in these patients were assigned to each variable.*

Variables	**Patient frequency [n, %]**	**No to low ADR (n=37)**	**Moderate to severe ADR (n=42)**
≥4 comorbid conditions	35 (44.3)	7 (20.0)	28 (80.0)
Heart failure	23 (29.1)	6 (26.1)	17 (73.9)
Liver disease	3 (3.8)	0 (0%)	3 (100%)
No. of drugs [n]			
5-7	22 (27.8)	16 (72.7)	6 (27.3)
≥ 8	48 (60.8)	14 (29.2)	34 (70.8)
Previous ADR	3 (3.8)	0 (0)	3 (100.0)
Renal failure	10 (12.7)	4 (40.0)	6 (60.0)
Number of potentially inadequate 1	14 (17.7)	8 (57.1)	6 (42.9)
antidepressants and antipsychotics [21] [n] 2	1 (1.3)	0 (0)	1 (100.0)
Serum-level above the therapeutic reference-range [18], but below the alert-level	23 (29.1)	6 (26.1)	17 (73.9)
Serum-level above the alert-level [18]	2 (2.5)	0 (0)	2 (100.0)

[12] Onder et al.; 2010
[18] Hiemke et al.; 2011
[21] Holt et al.; 2010
ADR= adverse drug reaction

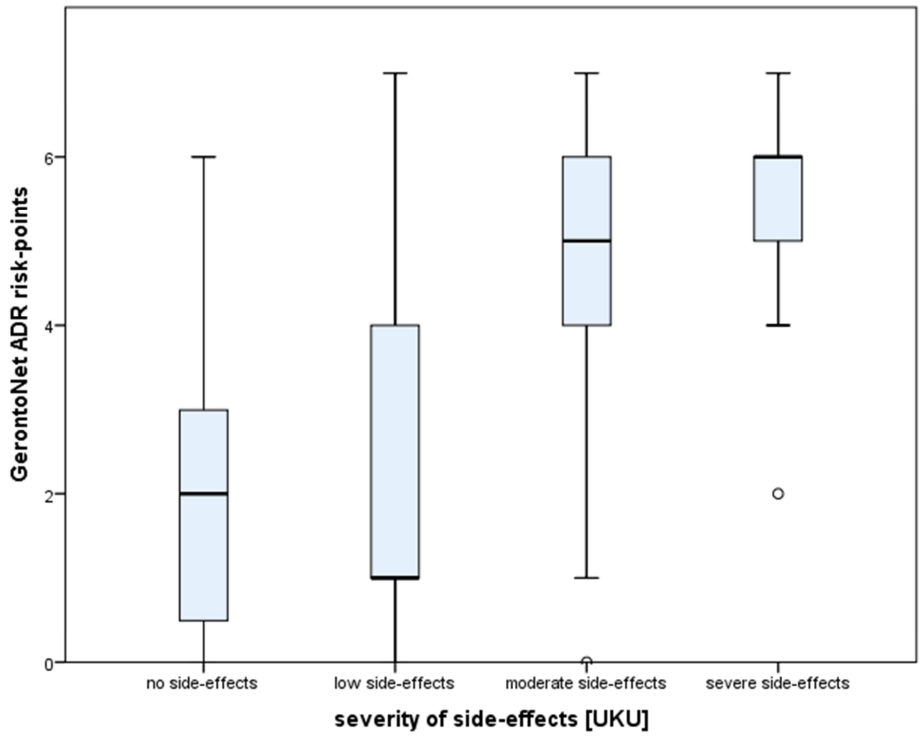

Figure 1. *Box plot of summated GerontoNet ADR risk points and severity of side-effects [UKU], evaluated in psychiatric selected inpatients ≥65 years (n=79) for whom a TDM has been requested. Overall, 7 patients (8.8%) showed no, 30 patients (38.0%) low, 33 patients (41.8%) moderate and 9 patients (11.4%) severe side-effects.*

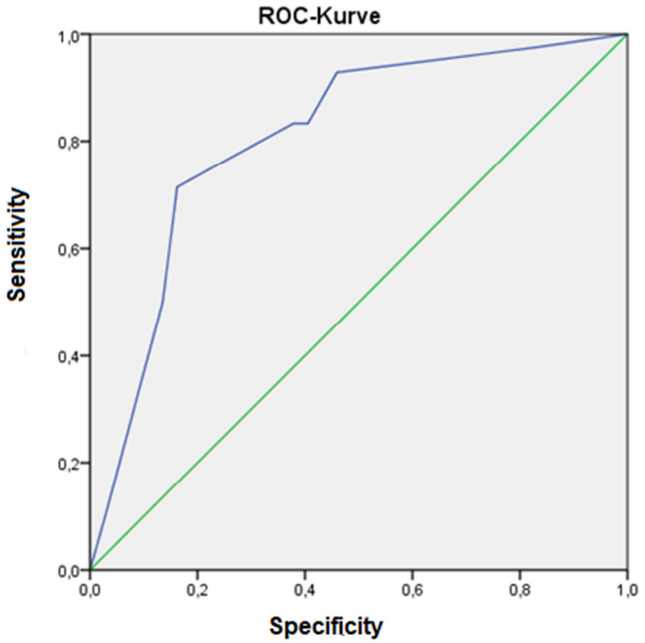

Figure 2. *Receiver operating characteristics (ROC) to identify patients ≥65 years (n=79) who are at high risk for moderate to severe ADRs. A threshold value between 4 and 5 was computed, (AUC=0.808; 0.708-0.908, 95% CI), predictive validity exhibited 71% sensitivity and 84% specificity.*

4. Discussion

To our knowledge, this is the first study that analyzed the applicability of the GerontoNet ADR risk score in a psychiatric setting. The risk scale [12] seemed to be a good predictor for ADRs, as GerontoNet ADR risk points correlated significantly (Figure 1) with observed ADRs ($r=0.525$, $p<0.01$, CI 95%). Predictive validity exhibited 71% sensitivity and 84% specificity for a newly evaluated threshold value between 4 and 5 to identify patients who are at high risk for moderate to severe ADRs (AUC=0.808, Figure 2). The predictive validity in the psychiatric setting seemed to be even higher, compared with previous studies that analyzed the validity of the score in other clinical settings [12, 13, 23]. In a study by Onder et al. [12], a threshold value between 3 and 4 was calculated to identify patients who are at high risk for ADRs. Sensitivity was 68%, specificity was 65% and the AUC in the validation study was 0.70. Furthermore, in accordance with results in this study, O´Connor and coworkers [13] analyzed in a non-psychiatric setting a median GerontoNet risk score of 5 in those patients who had an ADR and 3 in those without an ADR. Nevertheless, in the study by O´Connor et al. [13], 38% of patients were incorrectly classified as low risk. At last, in an external validation study in a non-psychiatric setting, Petrovic and colleagues [23] evaluated with a threshold value of 4 points very good sensitivity but poor specificity results in specific subgroups, e.g. older patients with a low body mass index or patients with osteoarthritis. Onder and coworkers [12] validated the GerontoNet risk score in hospitalized patients in geriatric and internal medicine wards. Inconsistent study-results can occur by applying variables of the GerontoNet ADR risk score in the psychiatric setting that differs markedly from the one in which the score was originally created and proposed for. Therefore, although predictive validity of the GerontoNet ADR risk score was satisfactory in this study, the utility of the score has to be scrutinized, as the predictive value of the GerontoNet ADR risk score is mainly based on the number of drugs ingested by the patient. Maximum summated risk score is 10 points, and 4 risk points were solely assigned to the intake of ≥8 drugs. Most of the patients in this study were polymedicated (Table 1, 3), and more than 60% of these took ≥8 drugs, they received by mean 8.8±3.9 drugs (range 1-18). Thus, 45.6% of the patients had attained 5 or more GerontoNet ADR risk points (Table 2). As the number of ingested drugs by a patient is a strong predictor for ADRs [12, 13, 17], it seemed plausible that more than 50% of patients in this study had moderate (41,8%) or severe (11,4%) ADRs (Table 1). Besides polypharmacy, a high prevalence rate of several other risk factors for the occurrence of ADRs could be detected in this study, as presented in table 3. These risk factors could lead to ADRs in a complex interplay and explain the high prevalence rate of ADRs in these vulnerable patients. In common, risk factors for the occurrence of ADRs differ markedly in the sort and in the prevalence rate in different study-settings, as presented by different studies [13]. As a result, the prevalence-rate of ADRs differs markedly in different study-setiings. Therefore, results of this study were not comparable with other studies. For example, Onder and coworkers [12], observed ADRs in only 11.6% of the patients who entered the validation study and O'Connor and colleagues [13] prospectively detected an ADR prevalence rate of 26% in acutely ill patients aged ≥65 years. In addition, they identified further variables that predict ADRs in hospitalised older people, as inappropriate medications and age ≥75 years. Tangiisuran and colleagues [11] detected in a teaching hospital an ADR prevalence rate of for about 14% in older hospitalized people. In addition, they identified hiperlipidaemia, raised white cell count, use of antidiabetic agents and length of stay ≥12 days as risk factors for developing an ADR [11]. Parameswaran and colleagues [10] detected the number of antihypertensives and presence of dementia as strongest predictors of an ADR.

We have three suggestions for changes in the score that were made below for the psychiatric setting.

4.1. Replacing the Variables of Liver Disease and Renal Failure with the Variable of too High Psychotropic Drug Serum Concentrations

In this study, a significant association between too high drug serum concentrations and the occurrence of ADRs was examined ($\chi 2 = 7.66$; $p<0.01$; OR: 4.27, 95% CI: 1.47-12.38). This result was expectable, as previous studies detected ADRs due to elevated drug blood levels in psychiatry before [19]. Therapeutic drug monitoring (TDM)

is a tool to control pharmacokinetic peculiarities [18, 19, 24], and therefore indicated to control e.g. individual age-related pharmakokinetic changes in elderly patients. Therefore, drug concentrations in blood were biomarkers for hepatic and renal drug clearance, as reviewed by Hefner and colleagues [19]. Accordingly, drug-serum levels above the therapeutic reference-range and notably above the alert-level may be a better indicator for the occurrence of ADRs in the psychiatric setting than diagnosis of hepatic and renal disease in the risk score by Onder et al [12]. Amongst others, ADRs due to pharmacokinetic drug-drug interactions, age-related pharmacokinetic changes, pharmacokinetic relevant comorbidities and genetic polymorphisms would all be considered with this variable [18, 19]. In this study, nearly one third (31.6%) of the patients developed serum levels above the therapeutic reference-range (Table 3), and 76% of them had moderate to severe ADRs. Contradictory, renal failure was only diagnosed in 12.7% and liver disease in 3.8% of the patients (Table 3).

4.2. Replacing the Variable of Heart Failure with the Variable of Number of Potentially Inappropriate Drugs

In the past, several tools have been developed for the purpose of medication appropriateness in the elderly [25], for example the Priscus-list [21]. Overall, the GerontoNET ADR risk score [12] does only consider the number but not the sort of drugs. Therefore, the use of potentially inappropriate drugs is not considered in the score. Prescribing of potentially inappropriate medication (PIMs) in the elderly is an important risk factor for ADRs, including a lot of inappropriate psychotropic medications [13, 21]. Especially in psychiatry, prescribing of these drugs should be avoided if more tolerable alternatives were available. Lists of PIMs include, amongst others, cardiac high-risk drugs, e.g. drugs with a high QT-time prolonging potential [21]. Therefore, we suggest to replace the variable of heart failure in the score by Onder and colleagues [12] with the variable of number of potentially inadequate drugs. In addition, lists of PIMs include amongst others drugs with high anticholinergic potential and fall risk increasing drugs [21]. Amongst others, falls are strongly associated with benzodiazepines, neuroleptics and antidepressants [26]. Furthermore, many psychotropic drugs have a high anticholinergic or QT-prolonging potential [27, 28]. Thus, by replacing the variable of heart failure with the variable of number of PIMs, different pharmacological high-risk drugs were considered. PIMs, as defined by the Priscus list [21], were taken in 67,1% of elderly patients in this study (Table 1). Thereof, potentially inadequate antidepressants and antipsychotics were taken in 15 cases (19.0%), and nearly half of the patients (n=7) developed moderate to severe ADRs (Table 3), in accordance with previous studies [16, 17] who investigated that antidepressants and antipsychotics are independent risk factors for ADRs. Because of the high prevalence rate of heart failure in elderly patients in this study (29,1%, Table 3), especially drugs with cardiac toxicity should be avoided. Of these patients, 73.9% developed moderate to severe ADRs.

4.3. Replacing the Variable of ≥4 Comorbid Conditions with the Variable of Frailty Syndrome

Frailtiness is an emerging public health priority, as frail elderly patients are extreme vulnerable to endogenous and exogenous stressors [29]. Fried and colleagues defined frailty as follows: a clinical syndrome in which three or more of the following criteria were present: unintentional weight loss (10 lbs in past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity [30]. It is a clinical syndrome that is associated amongst others with comorbidity and disability. Comorbidity is an etiologic risk factor for, and disability an outcome of frailty [30]. The frailty-syndrome may further increase the sensitivity of patients to develop ADRs [30]. Therefore, especially frail elderly patients need a comprehensive geriatric assessment [31] to guide complex pharmacotherapy. As reported in previous studies, frailtiness is highly prevalent in aged people and associated with an increased risk of falls, hospitalization and mortality [30, 32, 33]. Thus, the variable of frailty-syndrome is significantly associated with ADRs and should be integrated in the risk score. Especially in psychiatry, depression and frailty are highly prevalent and each condition is associated with an increased prevalence and incidence of the other [34]. Frailtiness is not present in all elderly patients, but associated with aging [35]. Non-frailty people can have several comorbid conditions that are not clinically relevant for the occurrence of ADRs, and frailty vulnerable people may have <4 comorbid conditions and might be overseen in the risk score. Therefore, the risk variable of frailty-syndrome should replace the variable of ≥4 comorbid conditions, as comorbidity is a risk factor for frailtiness. In this study, 44.3% of the elderly patients had at least four chronic comorbidities. Thereof, 80% developed moderate to severe ADRs (Table 3). In this regard, psychiatric elderly patients were often but not always frailty AND multimorbid.

4.4. Limitations

It has to be mentioned that the results of this study were not generalizable to the general psychiatric setting. Study population was restricted by elderly, often multimorbid and polypharmaceuted, psychiatric inpatients for whom TDM was requested. Included patients were therefore high-risk patients for the occurrence of an ADR. Therefore, selection bias could have confounded our results. In this regard, the utility of the GerontoNet ADR risk score should be examined especially in these commonly vulnerable patients the score was established for by Onder et al [12]. Multiplicity of different raters concerning severity and causality of ADRs could have also confounded the results of this study. As only one sample per patient was considered for evaluation, a patient-bias was avoided. Results of this study were also limited by the different interpretations of the GerontoNet risk variables [12]. Definitions of heart failure and liver disease

were not clearly defined by Onder and coworkers [12], so the results could be confounded by our own classification. In addition, measurement of GFR was retrospectively not possible and therefore renal disease was defined as diagnosis of any kidney disease in our study. Because of the fact that Onder and coworkers [12] included the intake of five drugs twice in the GerontoNet ADR risk score, we assigned one risk point to all patients who took 5 drugs. Consequently, calculation of the GerontoNet ADR risk score could vary between this study and the study by Onder et al [12] and therefore affect the results. The interpretation of the present results was further limited by the small sample-size (n=79) and by the naturalistic and the retrospective design of our study. Explorative data of a retrospective study do not prove any causal relationship.

5. Conclusions

Medical management becomes more and more complex with increasing age, and til date, numerous approaches [9] have been developed to improve pharmacotherapy in elderly patients, amongst others the GerontoNet ADR risk score [12]. The score seems to be a good predictor for patients who are at increased risk for an ADR in the psychiatric setting. However, this tool is mainly based on the number of drugs ingested by the patient and does not consider several further risk factors associated with ADRs in the psychiatric setting. In this study, as one important risk factor, a significant association between too high drug serum concentrations and the occurrence of ADRs was examined. For the psychiatric setting, we suggest 1. to replace the variables of liver disease and renal failure with the variable of too high psychotropic drug serum concentrations, 2. to replace the variable of heart failure with the variable of number of potentially inappropriate drugs 3. to replace the variable of ≥4 comorbid conditions with the variable of frailty syndrome in the GerontoNet ADR risk score [12]. However, single approaches, as the ADR risk score, can help the physician to assess the individual risk of psychopharmacological treatment in gerontopsychiatry, but comprehensive multifaceted geriatric assessment [8, 9] is always essential.

References

[1] Schneider EL, Campese VM. Adverse drug responses: An increasing threat to the well-being of older patients: Comment on "Development and validation of a score to assess risk of adverse drug reactions among in-hospital patients 65 years or older". Arch Intern Med. 2010 Jul 12; 170 (13): 1148-9. doi: 10.1001/archinternmed.2010.186.

[2] McLean AJ, Le Couteur DG. Aging biology and geriatric clinical pharmacology. Pharmacol Rev. 2004; 56 (2): 163-84. Epub 2004/06/01.

[3] Turnheim K. When drug therapy gets old: pharmacokinetics and pharmacodynamics in the elderly. Exp Gerontol. 2003; 38 (8): 843-53. Epub 2003/08/14.

[4] Fulton MM, Allen ER. Polypharmacy in the elderly: a literature review. J Am Acad Nurse Pract. 2005; 17 (4): 123-32. Epub 2005/04/12.

[5] Salive ME. Multimorbidity in Older Adults. Epidemiol Rev. 2013. Epub 2013/02/02.

[6] Mallet L, Spinewine A, Huang A. The challenge of managing drug interactions in elderly people. Lancet. 2007; 370 (9582): 185-91. Epub 2007/07/17.

[7] Beijer HJ, de Blaey CJ. Hospitalisations caused by adverse drug reactions (ADR): a meta-analysis of observational studies. Pharm World Sci. 2002; 24 (2): 46-54. Epub 2002/06/14.

[8] Petrovic M, van der Cammen T, Onder G. Adverse drug reactions in older people: detection and prevention. Drugs Aging. 2012 Jun 1; 29 (6): 453-62. doi: 10.2165/11631760-000000000-00000.

[9] Petrovic M, Somers A, Onder G. Optimization of Geriatric Pharmacotherapy: Role of Multifaceted Cooperation in the Hospital Setting. Drugs Aging. 2016 Mar; 33 (3): 179-88. doi: 10.1007/s40266-016-0352-7.

[10] Parameswaran Nair N, Chalmers L, Connolly M, Bereznicki BJ, Peterson GM, Curtain C, Castelino RL, Bereznicki LR. Prediction of Hospitalization due to Adverse Drug Reactions in Elderly Community-Dwelling Patients (The PADR-EC Score). PLoS One. 2016 Oct 31; 11 (10): e0165757. doi: 10.1371/journal.pone.0165757. eCollection 2016.

[11] Tangiisuran B, Scutt G, Stevenson J, Wright J, Onder G, Petrovic M, van der Cammen TJ, Rajkumar C, Davies G. Development and validation of a risk model for predicting adverse drug reactions in older people during hospital stay: Brighton Adverse Drug Reactions Risk (BADRI) model. PLoS One. 2014 Oct 30; 9 (10): e111254. doi: 10.1371/journal.pone.0111254. eCollection 2014.

[12] Onder G, Petrovic M, Tangiisuran B, Meinardi MC, Markito-Notenboom WP, Somers A, Rajkumar C, Bernabei R, van der Cammen TJ. Development and validation of a score to assess risk of adverse drug reactions among in-hospital patients 65 years or older: the GerontoNet ADR risk score. Arch Intern Med. 2010; 170 (13): 1142-8. Epub 2010/07/14.

[13] O'Connor MN, Gallagher P, Byrne S, O'Mahony D. Adverse drug reactions in older patients during hospitalisation: are they predictable? Age Ageing. 2012 Nov; 41 (6): 771-6. doi: 10.1093/ageing/afs046. Epub 2012 Mar 28.

[14] Hamzaoui A, Joulié A, El Dachri Y. [Polypharmacy and geriatric psychiatry]. Soins Gerontol. 2017 Sep - Oct; 22 (127): 17-21. doi: 10.1016/j.sger.2017.06.007.

[15] Hefner G, Unterecker S, Ben-Omar N, Wolf M, Falter T, Hiemke C, Haen E. Prevalence and type of potential pharmacokinetic drug-drug interactions in old aged psychiatric patients. CBHC. 2015 Jul.

[16] Bates DW, Miller EB, Cullen DJ, Burdick L, Williams L, Laird N, Petersen LA, Small SD, Sweitzer BJ, Vander Vliet M, Leape LL. Patient risk factors for adverse drug events in hospitalized patients. ADE Prevention Study Group. Arch Intern Med. 1999; 159 (21): 2553-60. Epub 1999/11/2

[17] Field TS, Gurwitz JH, Avorn J, McCormick D, Jain S, Eckler M, Benser M, Bates DW. Risk factors for adverse drug events among nursing home residents. Arch Intern Med. 2001; 161 (13): 1629-34. Epub 2001/07/24

[18] Hiemke C, Bergemann N, Clement HW, Conca A, Deckert J, Domschke K, Eckermann G, Egberts K, Gerlach M, Greiner C, Gründer G, Haen E, Havemann-Reinecke U, Hefner G, Helmer R, Janssen G, Jaquenoud E, Laux G, Messer T, Mössner R, Müller MJ, Paulzen M, Pfuhlmann B, Riederer P, Saria A, Schoppek B, Schoretsanitis G, Schwarz M, Gracia MS, Stegmann B, Steimer W, Stingl JC, Uhr M, Ulrich S, Unterecker S, Waschgler R, Zernig G, Zurek G, Baumann P. Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017. Pharmacopsychiatry. 2017 Sep 14. doi: 10.1055/s-0043-116492. [Epub ahead of print]

[19] Hefner G, Laib AK, Sigurdsson H, Hohner M, Hiemke C. The value of drug and metabolite concentration in blood as a biomarker of psychopharmacological therapy. Int Rev Psychiatry. 2013; 25 (5): 494-508. Epub 2013/10/25.

[20] Lingjaerde O, Ahlfors UG, Bech P, Dencker SJ, Elgen K. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. Acta Psychiatr Scand Suppl. 1987; 334: 1-100.

[21] Holt S, Schmiedl S, Thurmann PA. Potentially inappropriate medications in the elderly: the PRISCUS list. Dtsch Arztebl Int. 2010; 107 (31-32): 543-51. Epub 2010/09/10.

[22] Schmitt G., Herbold M., Peters F. Methodenvalidierung im forensisch-toxikologischen Labor. Auswertung von Validierungsdaten nach den Richtlinien der GTFCh mit VALISTAT. Walldorf: Arvecon; 2003.

[23] Petrovic M, Tangiisuran B, Rajkumar C, van der Cammen T, Onder G. Predicting the Risk of Adverse Drug Reactions in Older Inpatients: External Validation of the GerontoNet ADR Risk Score Using the CRIME Cohort. Drugs Aging. 2017 Feb; 34 (2): 135-142. doi: 10.1007/s40266-016-0428-4.

[24] Lundmark J, Bengtsson F, Nordin C, Reis M, Walinder J. Therapeutic drug monitoring of selective serotonin reuptake inhibitors influences clinical dosing strategies and reduces drug costs in depressed elderly patients. Acta Psychiatr Scand. 2000; 101 (5): 354-9. Epub 2000/05/24

[25] Chang CB, Chen JH, Wen CJ, Kuo HK, Lu IS, Chiu LS, Wu SC, Chan DC. Potentially inappropriate medications in geriatric outpatients with polypharmacy: application of six sets of published explicit criteria. Br J Clin Pharmacol. 2011 Sep; 72 (3): 482-9. doi: 10.1111/j.1365-2125.2011.04010.x.

[26] Davies EA, O'Mahony MS. Adverse drug reactions in special populations - the elderly. Br J Clin Pharmacol. 2015 Oct; 80 (4): 796-807. doi: 10.1111/bcp.12596. Epub 2015 May 22.

[27] Woosley RL, Heise, CW and Romero, KA, www.Crediblemeds.org, QTdrugs List, Accession Date 10.10.2017, AZCERT, Inc. 1822 Innovation Park Dr., Oro Valley, AZ 85755.

[28] Duran CE, Azermai M, Vander Stichele RH. Systematic review of anticholinergic risk scales in older adults. Eur J Clin Pharmacol. 2013. Epub 2013/03/27.

[29] Cesari M, Prince M, Thiyagarajan JA, De Carvalho IA, Bernabei R, Chan P, Gutierrez-Robledo LM, Michel JP, Morley JE, Ong P, Rodriguez Manas L, Sinclair A, Won CW, Beard J, Vellas B. Frailty: An Emerging Public Health Priority. J Am Med Dir Assoc. 2016 Mar 1; 17 (3): 188-92. doi: 10.1016/j.jamda.2015.12.016. Epub 2016 Jan 21.

[30] Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001 Mar; 56 (3): M146-56.

[31] Hilmer SN, McLachlan AJ, Le Couteur DG. Clinical pharmacology in the geriatric patient. Fundam Clin Pharmacol. 2007 Jun; 21 (3): 217-30.

[32] Shamliyan T, Talley KM, Ramakrishnan R, Kane RL. Association of frailty with survival: a systematic literature review. Ageing Res Rev. 2013 Mar; 12 (2): 719-36. doi: 10.1016/j.arr.2012.03.001. Epub 2012 Mar 12.

[33] Dani M, Owen LH, Jackson TA, Rockwood K, Sampson EL, Davis D. Delirium, frailty and mortality: interactions in a prospective study of hospitalized older people. J Gerontol A Biol Sci Med Sci. 2017 Nov 1. doi: 10.1093/gerona/glx214. [Epub ahead of print]

[34] Soysal P, Veronese N, Thompson T, Kahl KG, Fernandes BS, Prina AM, Solmi M, Schofield P, Koyanagi A, Tseng PT, Lin PY, Chu CS, Cosco TD, Cesari M, Carvalho AF, Stubbs B. Relationship between depression and frailty in older adults: A systematic review and meta-analysis. Ageing Res Rev. 2017 Jul; 36: 78-87. doi: 10.1016/j.arr.2017.03.005. Epub 2017 Mar 31.

[35] Ahmed N, Mandel R, Fain MJ. Frailty: an emerging geriatric syndrome. Am J Med. 2007 Sep; 120 (9): 748-53.