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Research Article

Rating The Delirogenic Potential of Drugs for Prediction of Side Effects in Elderly Psychiatric Inpatients

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Abstract

Background

Delirogenic potential of medications, especially anticholinergic properties, may give rise to adverse drug reactions (ADRs) in old aged patients. Objectives of the study were to assess a risk scale for rating of delirogenic properties of drugs and compare theoretical risks with observed side effects in old aged psychiatric inpatients.

Methods

From psychiatric patients aged ≥60 years for whom therapeutic drug monitoring (TDM) had been requested, medical files were analysed for prescribed medications with delirogenic activity. Based on these properties reported in the literature, primarily anticholinergic activity, a graded risk scale ranging from 1 (minimal) to 4 (high) was established for 106 drugs. From all drugs patients had received, a total risk score was calculated. The severity of occurring side effects was rated using the UKU (Udvalg for Kliniske Undersøgelser) scale.

Results

A group of 69 inpatients (63.8% female) with a mean age ± SD of 74.3±5.7 years was available for analysis. Patients attained by mean a risk score of 4.6±2.8 (range 0-15) according to their medications. Risk scores correlated significantly with observed side effects. Spearman correlation coefficient was 0.733 ($P<0.01$, CI 95%). An increased risk for side effects was found for a risk score of at least 5 (AUC= 0.893).

Conclusions: Since drug induced delirium is an underestimated scourge in the geriatric population and delirogenic properties

of drugs were highly predictive for occurring side effects, it is recommended to implement a risk scale like ours in the planning of psychopharmacological treatment of old aged patients for improved safety.

Keywords: Delirium; Risk Scale; Anticholinergic Effects; Psychopharmacology; Gerontopsychiatry; Pharmacodynamics

Introduction

Providing medical care for aging patients presents challenges, because these patients are at risk of comorbidities and polypharmacy [1]. Many commonly prescribed drugs for them have delirogenic, especially anticholinergic activity [2-5]. Awareness of these properties is considered to increase the safety of pharmacotherapy.

The central nervous system (CNS) of older patients ≥65 years is more sensitive to the anticholinergic activity of drugs than of younger patients due to age-related pharmacodynamic and pharmacokinetic changes [4,6], leading to CNS related adverse drug reactions (ADRs) such as impairment of cognitive functions, agitation and sedation, and peripheral effects such as tachycardia, dry mouth, constipation, visual impairments, or urinary retention [4].

ADRs are often the result of the cumulative CNS toxic burden of multiple drugs and not due to a single compound [4]. It was reported [29] that nearly 60% of nursing-home residents and 23% of older people living in the community received one or more drugs with anticholinergic properties. Antipsychotics, antidepressants, antihistamines, and anticholinergic drugs themselves are the major drug-classes with anticholinergic activity [3,7]. Other drugs may induce delirium by dehydration (e.g. loop diuretics) or sedation (e.g. benzodiazepines) [8]. Because of the high number of medications with anticholinergic potential, patients who receive psychotropic drugs are at high risk for anticholinergic ADRs [4,8].

A drug induced delirium depends on the agents and their doses and concentrations in blood [9]. Chew and colleagues (2008) measured the anticholinergic activity (AA) of 107 drugs that are commonly used by older adults *in-vitro*. An increase in dosage or serum-concentration of drugs with anticholinergic potential resulted in an increase in the AA. Measuring serum-concentrations of drugs with delirogenic properties, i.e. therapeutic drug monitoring (TDM) [10], is suitable to minimize the delirogenic load of prescribed medications, especially when alternative drugs are not available. To avoid excessive exposure, however, it is important to check side effect burdens of planned medications [5,11]. Providing a pharmaceutical care plan with the prevention of drug-related problems is a key issue in treatment of old aged patients. A scale that evaluates the delirogenic risk of drugs could help the physician in the medication-management for older patients.

Several scales for quantification of the drug related anticholinergic burden have been developed [7,8,12,13,14]. These lists differ in the setting in which the scale was established and in the evaluation of the anticholinergic potency of the drugs. We amalgamated these lists and defined delirogenic risk scores of 1 to 4 for 106 drugs to calculate the theoretical risk of applied medications. For evaluation we compared calculated risk scores with observed side effects in medicated old aged psychiatric patients. The primary aim was to find out if there is a positive correlation between risk scores and severity of delirium associated side effects.

Patients and Methods

Patients

The present retrospective study included data from psychiatric patients with age older than 60 years and for whom blood level measurements of the administered psychotropic drug were requested in the period between April 2011 and October 2012 at the Department of Psychiatry and Psychotherapy, University Medical Center Mainz, Germany. Retrospective analysis of clinical data for this study was in accordance with regulations given by the local ethics committee of the Ärztekammer Rheinland-Pfalz. These patients were diagnosed according to International Classification of Mental and Behavioral Disorders, 10th Revision (ICD-10) and their medical records were screened for anticholinergic side effects due to psychopharmacological treatment. No restriction was made with respect to age, gender, diagnosis, severity of illness, treatment-time or co-medication.

Patients were excluded when evaluation of a causal relationship [15] of possible drug-induced side effects was not possible, for example because of acute detoxification, intoxication, severe dementia, diagnosis of psychosis, somatic disorders such as moderate to severe illness of the prostate or bacterial or viral infection at the time of blood-withdrawal. Patients who were either delirious upon initial assessment, with insufficient data in their medical records, were non-compliant or had serum-levels of psychotropic drugs above their therapeutic reference-range at the time of blood-withdrawal were also excluded [10].

Risk-scale for delirogenic properties

An established list and classification for anticholinergic properties of drugs of the German pharmacovigilance group AGATE (Arbeitsgemeinschaft Arzneimitteltherapie bei psychiatrischen Erkrankungen) [8] was adapted to be used as a scale in clinical practice. We also considered anticholinergic properties as done by [7] and broadened the spectrum of drugs as classified by [14]. In addition we integrated clinical aspects of potential delirogenic drugs as done by [12]. Furthermore, potential anticholinergic properties of drugs of the AGATE-list [8]

and the Priscus list [3] were considered and integrated in our scale as "delirogenic". Moreover, biperiden which is a commonly prescribed anticholinergic drug in psychiatry (Pullen et al., 1984) [17] was added.

Table 1. Risk scale for 106 drugs with a differential delirogenic potential, primarily based on anticholinergic properties of drugs reported in the literature.

Drug	Risk-points	Drug	Risk-points	Drug	Risk-points
Alprazolam	1	Dipyridamole	1	Oxazepam	1
Amantadine	1	Donepezil	1	Oxcarbazepine	2
Amitriptyline	4	Doxepin	4	Oxybutynin	3
Amoxicillin	1	Duloxetine	1	Oxycodone	1
Ampicillin	1	Escitalopram	2	Paroxetine	3
Atropine	4	Fentanyl	1	Perphenazine	1
Baclofen	1	Flunitrazepam	1	Pethidine	1
Biperiden	4	Fluoxetine	2	Phenytoin	1
Bromazepam	1	Fluphenazine	1	Pimozide	2
Brotizolam	1	Flurazepam	1	Prazepam	1
Captopril	1	Fluvoxamine	1	Prednisone	1
Carbamazepine	2	Furosemide	1	Procyclidine	4
Celecoxib	1	Gentamicin	1	Promethazine	4
Cephalexin	1	Hydralazine	1	Quetiapine	2
Chlordiazepoxide	1	Hydrocodone	1	Ranitidine	2
Chlorphenamine	4	Hydroxyzine	4	Scopolamine	4
Cimetidine	2	Imipramine	4	Sertraline	1
Citalopram	2	Lansoprazole	1	Temazepam	2
Clemastine	4	Levofloxacin	1	Tetrazepam	1
Clindamycin	1	Levomepromazine	4	Theophylline	2
Clobazam	1	Lithium	2	Thioridazine	4
Clomipramine	4	Lorazepam	1	Tolterodine	4
Clonazepam	1	Lormetazepam	1	Topiramate	1
Clonidine	1	Maprotiline	4	Tramadol	1
Clorazepate	1	Medazepam	1	Triamcinolone	1
Clozapine	4	Metformin	1	Triamterene	1
Codeine	1	Methylprednisolone	1	Triazolam	1
Colchicine	4	Mirtazapine	2	Trihexyphenidyl	4
Dexamethasone	1	Morphine	1	Trimipramine	4
Diazepam	1	Nifedipine	1	Triprolidine	1
Digoxin	1	Nitrazepam	1	Valproic acid	1
Diltiazem	1	Nortriptyline	3	Vancomycin	1
Dimenhydrinate	4	Olanzapine	3	Warfarin	1
Dimetindene	1	Opipramol	4	Zaleplon	1
Diphenhydramine	3	Orphenadrine	4	Zolpidem	1
				Zopiclone	1

Delirogenic properties were categorized by the authors as minimal (1), low (2), moderate (3) or high (4) in accordance with the rating scale of [7] for anticholinergic properties. The list of Chew and co-workers (2008) was extended by amalgamation with lists of other investigators [3,18,12,14]

For grading of delirogenic properties, we used the classification of [7] who measured *in-vitro* anticholinergic activity (AA) of 107 medications commonly prescribed to older adults. Chew et al. thus defined 68 drugs with no, 17 drugs with minimal, 8 drugs with low, 6 drugs with moderate and 8 drugs with high AA [7].

Drugs with minimal AA according to [7] received one risk-point, drugs with low AA received 2 risk-points, drugs with moderate AA received 3 risk-points and drugs with a high AA received 4 risk-points in our risk-scale. Drugs listed by [7]

were supplemented with drugs evaluated by other investigators [12,14] who also classified the AA of drugs in four different levels. In cases of discrepancies between different drug scales in the evaluation of the anticholinergic potential of the drug, the grading of [7] was preferred. Because the measured AA was prioritized in our scale, results from the study of [14] were privileged in the risk-scale when they differed from the grading by [12]. Because of its strong anticholinergic property biperiden, sometimes required for therapeutic reasons, received 4 risk-points [17]. Finally, one risk-point was given to potential delirogenic drugs which were not mentioned in the above mentioned studies but in the AGATE (Back et al., 2011) [8] or Priscus list [3].

In summary, risk points found in table 1 were defined as follows:

1 risk-point: no delirogenic activity under therapeutic doses. Minimal delirogenic activity under supratherapeutic doses,

2 risk-points: low delirogenic activity under therapeutic doses,

3 risk-points: moderate delirogenic activity under therapeutic doses,

4 risk-points: high delirogenic activity under therapeutic doses.

All drugs taken by the patients were rated. No points were given to drugs not mentioned in Table 1.

Clinical assessment

An analysis of delirium associated side effects documented on TDM request forms and in the medical records was conducted around the period of blood withdrawal for each patient. The analysis identified typical anticholinergic adverse effects reported on the TDM request forms and in the medical files. Hyposalivation, dizziness, confusion, cognitive impairment, constipation, accommodation disturbances, urinary retention, blood pressure disturbances, tachycardia and falls, restlessness, excitation and delirium were attributed to anticholinergic / delirogenic drug effects.

Request forms and medical records contained information on clinical assessments. The causality and severity of the entity of occurred side effects around the time of blood-withdrawal were rated using the UKU (Udvalg for Kliniske Undersøgelser) rating-scale [16]. The severity of side effects was graded by a 4-point-scale (0= no ADRs, 1= low ADRs, 2= moderate ADRs, 3= severe ADRs). The causality assessment of a possible drug induced ADR was made on the basis of clinical judgment of the physician by a 3-point scale. The physician decided if causality was implausible, possible, or probable. If ADRs were mentioned in the medical record without grading by the physician, a clinical pharmacist evaluated the severity and causality retrospectively based on the available data.

Evaluation of the risk-scale

Drugs were listed as chronic and needed medications received on the day of blood withdrawal. The delirogenic burden of each medication was rated using the risk-scale. Total individual burden (risk score) of the patient was determined by summarizing the risk points of all drugs received by a single subject and listed in the risk scale. Topical, ophthalmic, inhaled, and otologic preparations were excluded from the calculation. If a drug was received as a scheduled medication and also as needed medication, its rating was included once. Only one sample per patient was included in the study. In the case of multiple determinations of psychotropic drugs in the same patient only the last analysis was included.

From the medical record, further information about patient age, gender, diagnosis, duration of hospitalization, and comedication were collected. The total number of prescribed medications was calculated, excluding topical, ophthalmic, inhaled and otologic medications. Additionally, we calculated the number of potentially inappropriate drugs according to the Priscus List [3] for each patient.

Data management and statistical analysis

Possible correlations between the risk-score and severity of ADRs (UKU) were determined by using Spearman´s correlation analysis. In addition, calculated risk-scores were plotted against the severity of ADRs (UKU). In order to evaluate the threshold risk-score level above which patients are expected to obtain anticholinergic ADRs, a receiver operator characteristic (ROC) curve was constructed, and the area under the curve (AUC) was calculated. Statistical analysis was carried out using IBM® SPSS® Statistics version 20.0 (IBM GmbH, Ehningen, Germany). A P-value <0.05 was considered as statistically significant.

Results

In total, a group of 117 patients was available for analysis. After excluding patients with insufficient information, 69 patients could be analyzed (Table 2). The most frequent diagnoses according to ICD-10 were a recurrent depressive disorder with a severe current episode (N=31, 44.9%) without psychotic symptoms (F33.2) followed by a severe depressive episode (N=10, 14.5%) without psychotic symptoms (F32.2).

Patients received by mean±SD 8.2±4.1, including 0.9±0.9 potentially inappropriate drugs [3].

The mean calculated risk score of the drugs was 4.6±2.8 as shown in table 3. In 59.5% of the cases, no delirium associated side effects were protocoled in the medical file. Mean UKU severity-index of side effects was 0.75±1.02 at which 0= no,

Table 2. Patients' characteristics.

		Samples (n Total; %)	Min-Max	Mean (±SD)
Number of patients [n]		69 (100.0)	N/A	
Age [n]		69 (100.0)	63-89	74.3±5.7
Gender [n]	**female**	44 (63.8)	N/A	
	male	25 (36.2)		
Risk-score[n]		69 (100.0)	0-15	4.6±2.8
Potentially inappropriate drugs [n]		69 (100.0)	0-4	0.9±0.9
Number of medications per patient [n]		69 (100.0)	1-17	8.2±4.1
Duration of hospitalization [days]		69 (100.0)	4-151	52.2±31.9
Severity of adverse drug reactions (UKU) [n]	none	41 (59.5)	N/A	
	mild	9 (13.0)		
	moderate	14 (20.3)		
	severe	5 (7.2)		

1= low, 2= moderate, and 3= severe.

UKU, (Udvalg for Kliniske Undersogelser) side effects rating scale

Table 3. Delirogenic burden (risk-points) in 69 elderly psychiatric inpatients.

		Frequency	Percent
Risk-points	**0**	2	2.9
	1	3	4.3
	2	16	23.2
	3	7	10.1
	4	7	10.1
	5	9	13.0
	6	10	14.5
	7	8	11.6
	8	2	2.9
	9	3	4.3
	13	1	1.4
	15	1	1.4
	Total	**69**	**100.0**

The most commonly mentioned side effects in the medical files were blood pressure disturbances and dizziness (n=11, 19.3%) resulting in falls in two cases (3.5%). CNS toxicity (disorientation, cognitive decline) occurred in eleven cases (19.3%). Constipation (n=10, 17.5%), restlessness and excitation (n=10, 17.5%) and hyposalivation (n=7, 12.3%) were also frequent.

Two women (3.6%) had acute severe and one woman (1.8%) moderate urinary retention. Failure of accommodation and hyperthermia occurred in each case (1.8%). One 86 years old patient with 12 risk-points became delirious.

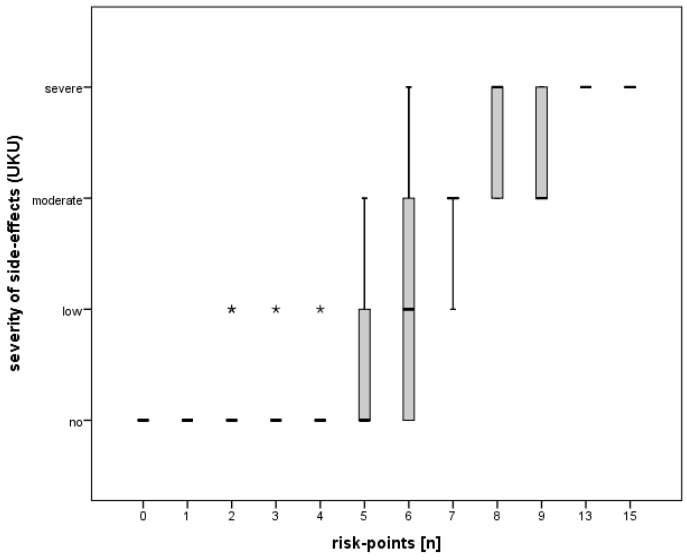

Figure 1. Box plots of delirogenic burden (risk-score) and severity of adverse drug reactions (UKU), evaluated in 69 older psychiatric inpatients.

The most frequently prescribed drugs of the risk scale were mirtazapine (50.7%) and lorazepam (61.2%), followed by diazepam, quetiapine and zopiclone (13.4%), citalopram and

nortriptyline (11.9%). According to the risk-scale, 8.6% of the drugs with therapeutic dosage had a high delirogenic activity of 4 risk-points, 7.9% a moderate activity of 3 risk-points and 34.1% a low activity (2 risk-points) while 49.4% of the patients had delirogenic activity only under supratherapeutic doses (1 risk-point).

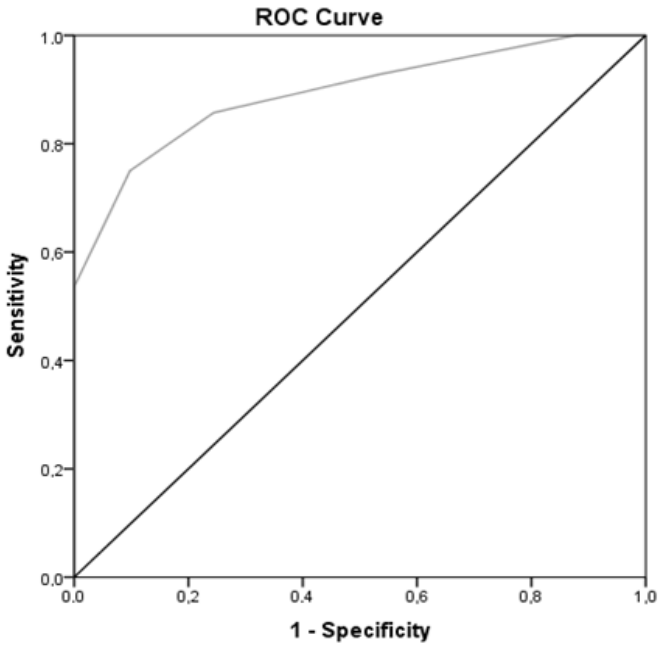

Figure 2. Receiver operating characteristics (ROC) analysis for an increased risk of delirogenic side effects indicated by a risk score in 69 old aged psychiatric inpatients. A significantly increased risk for side effects was associated with 4.5 or more risk-points (AUC= 0.893). The area under the ROC curve was 0.893 (95% CI, 0.811-0.975).

It was found that risk-score correlated significantly with the observed side effects as shown in figure 1. Spearman correlation-coefficient was 0.733 (P<0.01, CI 95%). A lower threshold associated with an increased risk for side effects was computed by ROC analysis (Figure 2), resulting in 4.5 points. For this value, a predictive validity exhibited 86% sensitivity and 76% specificity. The area under the ROC curve was 0.893 (95% CI, 0.811-0.975).

Discussion

The primary aim of this study was to compare theoretical delirium associated properties of drugs, most of them anticholinergic properties, and occurring side effects. Regarding existing risk-scales for drugs with anticholinergic properties considerable variation is obvious in terms of the selection of drugs, anticholinergic potential of drugs and the clinical setting in which the scale was applied. The advantage of the established risk-scale is simplicity. Drugs were categorized in five different grades ranging from absent (0 points) to severe (4 points). The scale enabled quantification of delirogenic load of individual medications. Calculated sum scores correlated well with observed side effects known to be associated with delirogenic properties of drugs, mostly anticholinergic activity.

Our findings were consistent with studies of other investigators [18-20] who detected in a non-psychiatric setting an association between the calculated anticholinergic burden and the occurrence of ADRs. So far, however, only [21] measured anticholinergic activity using a risk scale in psychiatric patients. The mean age of the 83 patients and gender distribution was similar as in our sample. For evaluation, three different expert based scales were used by [21], the anticholinergic risk scale (ARS) [20], the anticholinergic drug scale (ADS) [14] and the anticholinergic cognitive burden scale (ACB) [22]. The average anticholinergic burden was 1.98±1.3 calculated with ADS, 1.96±1.01 with ARS and 3.28±1.58 with ACB. The agreement between the three scales, however, was rather poor.

[20] found that 70% of the patients reported anticholinergic adverse effects when their total score was 3 or higher. Furthermore, [23] reported that the total risk of anticholinergic effects increased when the score calculated with ARS [20] and ADS [14] was ≥3 in both scales. Conversely, this threshold did not apply for central effects [24]. A study by [24] found no cognitive decline with ADS [14] scores above 3 and concluded a limited potential of the ADS to predict the clinical risk of central anticholinergic side effects in frail older patients. However, the risk-score of ≥3 calculated with the ARS and the ADS [23] cannot be compared with the lower calculated threshold of approximated 5 risk-points using the risk-scale that has been established in this study.

Altogether, previous studies [15,18,19,23,24,25,26,27] differ in methodology applied in the development of each scale, in clinical setting and methods of ADRs evaluation.

Delirogenic properties calculated by our rating scale correlated well with occurring side effects. Our rating scale thus has the potential to predict side effects. We were able to calculate by ROC analysis a lower threshold score that was associated with an increased risk for anticholinergic ADRs of approximately 5 risk-points. The prevalence for side effects was 47.7% for patients with a risk score of 5 points or higher. In our sample, the highest prevalence for side effects was found under medications with 1 risk point. This is consistent with observations made by other investigators that polypharmacy is an independent risk factor for delirium in a population of elderly patients [18].

Limitations

Our study has several limitations. The number of patients whose data could be used for retrospective analyses (n= 69) limited the strength of this study. Nevertheless, the highly significant correlation between calculated risk points and

observed side effects points to a robust finding. Duration of treatment with the administered drugs was not considered. In addition, compliance of drug-intake was limited to the psychotropic drugs for which a serum level measurement was requested. Non-compliance to take other medication could have confounded our results because anticholinergic burden of a patient was overestimated. Patients' predisposing for delirium due to their morbidity [30] was not considered which would have been of interest for causality assessment side effects in our study. The scale does not consider drug doses. For a full estimation of the anticholinergic burden in older adults, the dosage, or even better serum-concentration, should be taken in consideration. Since anticholinergic activity depends on the serum-level of the drugs [7,9], the risk-scale may be extended when used in combination with TDM.

The retrospective assessment of occurring side effects was based on physicians' and nursing staff comments in the medical-file and on the request form. The UKU rating scale used here and being implemented on the request form is an assessment scale for the severity side effects. However, it does not consider frequency. In clinical practice, there may be variable effects of anticholinergic peripheral and central adverse effects to the same time. Some especially mild anticholinergic ADRs may be overseen by the physician or the caregivers and therefore not be protocolled in the medical-files. Therefore, the occurrence of side effects may be underestimated in this study.

Conclusions

Since the theoretical risk scores correlated well with reported side effects of the patients, it may be assumed that the risk score is predictive for delirium associated side effects that may be expected under pharmacotherapy. The risk scale can be easily applied as a tool to plan pharmacotherapy for older psychiatric patients. Implementing the scale could aid the physicians to assess the individual risk of psychopharmacological treatment and consequently improve the safety of pharmacotherapy in gerontopsychiatry. Future studies with higher sample sizes are needed to confirm our observation and analyze if the use of the risk scale for medication planning can improve drug tolerability in psychiatric older patients.

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