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Risiken in der Arzneimitteltherapie von multimorbiden älteren Patienten und deren Einfluss auf die Arzneimitteltherapiesicherheit anhand der Daten der MultiCare Studie

Dissertation

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Inhaltsverzeichnis

Abkürzungsverzeichnis

ACB	Anticholinergic Burden – deutscher Anticholinergika Score
ADS	Anticholinergic Drug Scale
ADS/P	„anxiety, depression, somatoform disorders and pain“
ATC	Anatomical Chemical Classification
CMD	„cardiovascular and metabolic disorder cluster“
D-CDH	Arzneistoffe für koronare Herzkrankheiten und Hypertonie - Drugs for Coronary Diseases and Hypertension
D-DG	Diuretika und Arzneistoffe bei Gicht - Diuretic Drugs and drugs for Gout
D-HF	Arzneistoffe für Herzinsuffizienz - Drugs for Heart Failure
D-OPD	Arzneistoffe für chronisch obstruktive Lungenerkrankungen - Drugs for chronic Obstructive Pulmonary Diseases
D-Osteo	Arzneistoffe gegen Osteoporose - Drugs for Osteoporosis
D-Pain	Arzneistoffe gegen Schmerzen - Drugs for Pain
EU(7)-PIM	Liste potentiell inadäquater Medikation, gültig für den europäischen Raum
FORTA	Fit fOR The Aged – Positiv-Negativ-Arzneimittelliste zur Identifizierung von potentiell inadäquater Medikation
ICD-10	International Statistical Classification of Diseases and Related Health Problems
LDST	Letter Digit Substitution Test
NPS	„neuropsychiatric disorders“
NSAID	Nichtsteroidales Antiphlogistikum (englisch: non-steroidal anti-inflammatory-drug)
OTC	over-the-counter – nicht verschreibungspflichtige Arzneimittel
PIM	potentiell inadäquate Medikation
PPI	Protonenpumpeninhibitoren
PRISCUS	Liste potentiell inadäquater Medikation, gültig für den Deutschen Raum
UAE	unerwünschtes Arzneimittelereignis

Verzeichnis eingeschlossener Publikationen

Publikation I

Krüger C, Schäfer I, van den Bussche H, Baehr M, Bickel H, Fuchs A, Gensichen J, Maier W, Riedel-Heller SG, König HH, Dahlhaus A, Schön G, Weyerer S, Wiese B, von Renteln-Kruse W, Langebrake C , Scherer M. Non-random relations in drug use expressed as patterns comprising prescription and over-the-counter drugs in multimorbid elderly patients in primary care – data of the exploratory analysis of the multicentre, observational cohort study MultiCare: Eur J Gen Pract. 2021 Jan 1;27(1):119–29

Pubklikation II

Krüger C, Schäfer I, van den Bussche H, Bickel H, Dreischulte T, Fuchs A, König HH, Maier W, Mergenthal K, Riedel-Heller SG, Schön G, Weyerer S, Wiese B, von Renteln-Kruse W, Langebrake C , Scherer M. Comparison of FORTA, PRISCUS and EU(7)-PIM list on identifying potentially inappropriate medication and its impact on cognitive function in multimorbid elderly German people in primary care: a multicentre observational study: BMJ Open. BMJ Open. 2021 Sep 1;11(9):e050344

Publikation III

Krüger C, Schäfer I, van den Bussche H, Bickel H, Fuchs A, Gensichen J, König HH, Maier W, Mergenthal K, Riedel-Heller SG, Schön G, Weyerer S, Wiese B, von Renteln-Kruse W, Langebrake C , Scherer M. Anticholinergic drug burden according to the anticholinergic drug scale and the German anticholinergic burden and their impact on cognitive function in multimorbid elderly German people: a multicentre observational study. BMJ Open. 2021 Mar 1;11(3):e044230

1. Synopse

1.1. Einleitung

1.1.1 Theoretischer Hintergrund

Bedingt durch den demografischen Wandel müssen wir uns immer mehr mit den Folgen einer Verschiebung der Altersstruktur beschäftigen. Laut Angaben des statistischen Bundesamts Deutschland sinken die Geburtenzahlen nachhaltig und gleichzeitig steigt derzeit die Lebenserwartung um 0,1 Jahre pro Jahr an [1]. Auch die Zuwanderung kann diesen Alterungsprozess der Bevölkerung langfristig nicht aufhalten [2]. Gemäß Demografiebericht des deutschen Bundesinnenministeriums werden bereits im Jahr 2060 34 % der Bevölkerung 65 Jahre und älter sein [2]. Im Vergleich waren es 2010 noch 21 % der Gesamtbevölkerung Deutschlands. Zusätzlich wird davon ausgegangen, dass 2050 jeder siebte Einwohner Deutschlands 80 Jahre und älter sein wird [2].

Obwohl Altern ein individueller Prozess ist, ist er gekennzeichnet durch Veränderung der physiologischen Organfunktion und von regulatorischen Prozessen. Speziell kommt es zur Veränderung in pharmakokinetischen Prozessen, wie ein erhöhter gastraler pH-Wert, eine verringerte Magen-Darm-Motilität, eine Veränderung der Körperzusammensetzung (Zunahme des Körperfettanteils), eine verminderte Albuminproduktion, eine verminderte hepatische Durchblutung, eine verminderte Aktivität der mikrosomalen Leberenzyme, ein reduzierter First-pass-Effekt, ein reduziertes Herzzeitvolumen, eine verminderte renale Elimination und damit verbunden auch eine reduzierte kardiale Leistung [3]. Aber auch die pharmakodynamischen Prozesse unterliegen Veränderungen im Alter. Diese sind zum Beispiel gekennzeichnet durch eine erhöhte Rezeptorsensibilität für zentral wirksame Arzneistoffe, eine verminderte cholinerge Transmission, Gangstörungen und dessen Folgen. Außerdem ist eine erhöhte Gebrechlichkeit zu beobachten [3–5].

1.1.2 Multimorbidität und Multimedikation

Gerade ältere Menschen haben ein erhöhtes Risiko an multiplen chronischen Erkrankungen zu leiden [6,7]. In Reviews wird eine Prävalenz von 21 % bis 100 % für Multimorbidität bei Patienten ab 65 Jahren berichtet [8,9]. Multimorbidität wird als das gleichzeitige Auftreten

von mehreren chronischen Erkrankungen definiert, wobei in Publikationen zu multimorbiden Patienten in der Regel von mindestens zwei chronischen Erkrankungen ausgegangen wird [10]. Multimorbidität ist unter anderem assoziiert mit einem Verlust der Selbständigkeit, einer verminderten Lebensqualität und einer erhöhten Mortalität der betroffenen Personen [11]. Darüber hinaus führt Multimorbidität oft zu Multimedikation, auch Polypharmazie genannt. Multimedikation ist die gleichzeitige Anwendung und/oder Verordnung von verschiedenen Arzneimitteln zur gleichen Zeit. Die meisten Studien definieren Multimedikation als die gleichzeitige Einnahme von fünf oder mehr Arzneimitteln zur gleichen Zeit [12–15]. Multimedikation wird oft verstärkt durch unerwünschte Arzneimittelereignisse (UAE) und Selbstmedikation, dies kann wiederum zu Verschreibungskaskaden führen. Weiterhin wurde festgestellt, dass Multimedikation das Risiko für UAE, Arzneimittelinteraktionen und Medikationsfehler erhöht [16–18]. Multimedikation führt deshalb häufig bei älteren Patienten zu einer Verminderung der Lebensqualität und gefährdet zusätzlich die Arzneimitteltherapiesicherheit der multimorbiden älteren Patienten [14,19,20]. Arzneimitteltherapiesicherheit beschreibt eine sichere Anwendung eines Arzneimittels über die Anwendungs- und Einnahmehinweise hinaus. Sie umfasst alle Maßnahmen zur Gewährleistung des bestimmungsgemäßen Gebrauches eines Arzneimittels mit dem Ziel den Medikationsprozess zu optimieren und Risiken in der Arzneimitteltherapie der Patienten zu reduzieren [21].

Im Rahmen der MultiCare Studie wurde Multimorbidität als das Auftreten von mindestens drei chronischen Erkrankungen definiert, um zu verhindern, dass nahezu jeder Patient über 65 Jahren als multimorbid eingestuft wird [22]. Ergebnisse von Schäfer et al. aus dieser Studie zeigten, dass die Patienten im Mittel 74,4 Jahre alt und zu 59,3 % weiblich waren, mit 62,3 % einen niedrigen Bildungsstand hatten und im Mittel ein monatliches Nettoeinkommen von 1412 € pro Haushalt zur Verfügung hatten. Basierend auf einer vorher festgelegten 46 ICD-10 Codes umfassenden Liste, wiesen die Patienten 7,0 (± 2,5) chronische Erkrankungen auf. In der Studienpopulation waren die häufigsten Diagnosen Hypertonie (Prävalenz: 77,9 %), Lipidstoffwechselstörungen (58,5 %) und chronische Rückenschmerzen (49,5 %) [23].

1.1.3 Risiken von potentiell inadäquater Medikation

Multimorbide ältere Patienten sind besonders anfällig für die Einnahme von potentiell inadäquater Medikation (PIM) [24]. Als PIM werden Arzneimittel bezeichnet die ein hohes

Risiko für UAE mit sich bringen und für die es eine sichere Alternative gibt. Hierzu zählen auch Arzneimittel mit schlechtem Nutzen-Risiko-Verhältnis oder Arzneimittel die keine gesicherte therapeutische Wirkung aufweisen [3,25]. Durch die altersbedingt veränderten pharmakokinetischen und pharmakodynamischen Prozesse, treten häufiger und auch verstärkt UAE auf [26,27]. Zusätzlich sind ältere Patienten besonders vulnerabel gegenüber durch potentiell inadäquate Medikation ausgelöste UAE [28]. Weiterhin geht die Einnahme von PIM unter anderem mit einem Risiko für eine reduzierte kognitive Funktion, eine erhöhte Gebrechlichkeit und einem vermehrten Auftreten von Stürzen einher [24].

Weltweit sind verschiedene Listen publiziert worden, mit denen PIM identifiziert und Alternativen im Arzneimittelgebrauch aufgezeigt werden können. Die Einstufung als PIM erfolgt dabei in der Regel auf Grund von epidemiologischen Studien, klinischer Erfahrung oder abgeleitet von dem pharmakologischen Wirkprinzip, da ältere Patienten in der Regel von Studien seitens der Pharmaindustrie ausgeschlossen werden. Eine häufig genutzte Methode ist die Delphi-Methode, bei der in einem mehrstufigen Befragungsverfahren mit Rückkopplung der Zwischenergebnisse, Experten anonym befragt werden [3]. Die erste publizierte und bekannteste Liste ist die amerikanische Negativliste von Beers aus dem Jahr 1991 [29]. Seit dem wurden viele weitere PIM-Listen entwickelt und veröffentlicht, welche man zum Teil den spezifischen Marktgegebenheiten und Verschreibungspraktiken der einzelnen Länder angepasst hat. Speziell für den deutschen Arzneimittelmarkt gibt es die FORTA-Liste (Fit fOR The Aged) und die PRISCUS-Liste (lateinisch: altehrwürdig) [25,30]. Zudem wurde eine allgemein gültige Liste für den europäischen Raum publiziert, die EU(7)-PIM-Liste [31]. Bei der FORTA-Liste handelt sich um implizite Kriterien. Es erfolgt eine indikationsabhängige Auswertung der Medikation eines Patienten, somit werden zur Anwendung unter Anderem individuelle Informationen über Erkrankungen der Patienten benötigt. Bei der PRISCUS- und EU(7)-PIM-Liste handelt es sich hingegen um explizite Kriterien, so dass keine zusätzlichen Informationen zur Beurteilung notwendig sind. Die einzelnen Listen unterscheiden sich zum Teil stark in ihren Schwerpunkten und hinsichtlich der aufgeführten Arzneistoffe. Einige zeigen Verordnungsszenarien auf, andere bewerten nach Kategorien und es werden zum Teil alternative Substanzen aufgezeigt oder Maximaldosierungen angegeben.

1.1.4 Risiken von Anticholinergika

Die Einnahme von Anticholinergika im Alter birgt ein erhöhtes Risiko für klassische anticholinerge Nebenwirkungen wie Verwirrtheit, Tremor, Sehstörungen, Delir, Mundtrockenheit und Harnverhalt [32]. Darüber hinaus erhöht diese unter anderem das Sturzrisiko, das Risiko eines Krankenhausaufenthalts, die Mortalität und auch ein Verlust der eigenen Selbstständigkeit der multimorbiden älteren Patienten ist in der Literatur beschrieben [33]. Zusätzlich soll der Gebrauch von Anticholinergika mit einer Reduktion der kognitiven Funktion und speziell der Entwicklung einer Demenz assoziiert sein [34,35]. Gerade multimorbide, ältere Patienten haben ein erhöhtes Risiko Anticholinergika oder Substanzen mit anticholinergen Nebenwirkungen einzunehmen [4]. Zusätzlich sind diese Patienten empfindlicher für anticholinerge UAE auf Grund einer altersbedingt verringerten cholinergen Übertragung und eines schlechteren Metabolismus und/oder einer schlechteren Elimination der Substanzen [36]. Neben klassisch anticholinerg wirkenden Substanzen (Arzneimittel bei Dranginkontinenz, chronisch obstruktiven Lungenerkrankungen oder Morbus Parkinson) führen zahlreiche Arzneimittel auch ohne ein primäres anticholinerges Wirkprinzip, bedingt durch eine Wirkung im zentralen Nervensystem, zu anticholinergen Nebenwirkungen. Dies wird durch die Antagonisierung des parasympathischen Nervensystems, bedingt durch die Bindung der Arzneistoffe an einen der fünf muskarinergen Rezeptoren im autonomen Nervensystem, hervorgerufen [5].

Die anticholinerge Last ist definiert als der kumulative Effekt, der durch die gleichzeitige Einnahme von Arzneistoffen mit anticholinerger Aktivität auftritt [37]. Zur Berechnung der individuellen anticholinergen Last eines Patienten wurden eine Reihe von Anticholinergika-Scores entwickelt, wie zum Beispiel der „Anticholinergic Drug Scale“ (ADS), der „Anticholinergic Risk Scale“ oder auch der „Anticholinergic Cognitive Burden Scale“ [38–40]. Speziell für den deutschen Arzneimittelmarkt gibt es bis jetzt noch keinen validierten Anticholinergika-Score. Jedoch wurde der deutsche „Anticholinergic Burden“ (ACB) von Kiesel et al. entwickelt um diese Lücke zu füllen und wird deshalb in der folgenden Arbeit mit untersucht [41]. Die meisten Scores basieren auf einem ähnlichen Prinzip. Arzneistoffen wird eine Wertung zwischen null und drei Punkten zugeordnet, wobei je nach Score unterschiedliche Bewertungsmechanismen zugrunde gelegt werden. Um die individuelle anticholinerge Last eines Patienten zu berechnen, summiert man die Punkte, die für die einzelnen Arzneistoffe vergeben werden, auf. Ein Wert von größer oder gleich drei bedeutet,

dass man alternative Arzneistoffe oder zumindest eine Dosisreduktion der problematischen Arzneistoffe erwägen sollte [40].

1.2 Fragestellung und Ziele

Eine adäquate Arzneimitteltherapie von multimorbiden älteren Patienten stellt immer noch eine große Herausforderung dar. Da unter anderem ältere Patienten oft von klinischen Studien ausgeschlossen werden, kann man existierende Leitlinien zum Teil nur schwer direkt bei älteren Patienten anwenden. Ziel der Promotionsarbeit war es deshalb, neue Erkenntnisse über die Arzneimitteltherapie und Arzneimitteltherapiesicherheit der multimorbiden älteren Patienten anhand des Patientenkollektivs der MultiCare Studie zu gewinnen. Es wurden folgende Projekte im Rahmen der Promotionsarbeit bearbeitet:

I. Charakterisierung des multimorbiden, älteren Patientenkollektivs hinsichtlich von Verordnungsmustern unter Verwendung von im „Brown-Bag“ Verfahren erfassten verschreibungspflichtigen und nicht verschreibungspflichtigen Arzneistoffen und Substanzen
II. Darstellung der Verwendung von potentiell inadäquater Medikation im Alter unter Verwendung der *FORTA-, PRISCUS*- und der *EU(7)-PIM-Listen.* Sowie Vergleich der europäischen EU(7)-PIM-Liste mit den beiden deutschen PIM-Listen FORTA und PRISCUS und die Bestimmung des Einflusses der Einnahme von potentiell inadäquater Medikation auf die kognitiven Fähigkeiten der multimorbiden älteren Patienten anhand eines großen und vermeintlich gesünderen Patientenkollektives
III. Berechnen der individuellen anticholinergen Last der multimorbiden, älteren Patienten und Darstellung der Assoziation zwischen individueller anticholinerger Last und kognitiver Funktion mittels erstmaligem Vergleich des validierten *„Anticholinergic Drug Scale“* mit dem deutschen *„Anticholinergic Burden“* anhand eines großen und vermeintlich gesünderen Patientenkollektives

So soll ein umfassendes Bild über das ältere multimorbide Patientenkollektiv geschaffen werden, um neue Informationen über die Arzneimitteltherapie und auch

Arzneimitteltherapiesicherheit dieser wachsenden und hoch vulnerablen Patientengruppe zu gewinnen.

1.3 Methodik

1.3.1 Prospektive longitudinale Kohortenstudie MultiCare

Grundlage für die folgenden Untersuchungen sind Daten aus der MultiCare Studie, einer multizentrischen, prospektiven, longitudinalen Kohortenstudie, die in 158 Hausarztpraxen in acht Studienzentren (Bonn, Düsseldorf, Frankfurt am Main, Hamburg, Jena, Leipzig, Mannheim und München) in Deutschland durchgeführt wurde. Ziel der Studie war unter anderem die Untersuchung der Folgen von Multimorbidität auf ältere Patienten in der hausärztlichen Versorgung. Dafür wurden sowohl Hausärzte, als auch ihre Patienten befragt. Patienten wurden eingeschlossen, wenn sie mindestens drei chronische Erkrankungen aufwiesen und zum Start der Studie zwischen 65 und 85 Jahre alt waren. Es wurden acht Ausschlusskriterien festgelegt: (I) Leben in einem Alten- oder Pflegeheim, (II) Blindheit, (III) Taubheit, (IV) Patienten mit diagnostizierter Demenz, (V) eine Lebenserwartung von weniger als drei Monaten, (VI) schlechte Deutschkenntnisse, (VII) Patienten die bereits an anderen Studien teilnehmen und (VIII) Patienten, die nicht regelmäßig ihrem Hausarzt aufsuchen. Von 50.786 Patienten, wurden 7172 Patienten nach Anwendung der Ein- und Ausschlusskriterien angeschrieben und um Einverständnis zur Teilnahme an der MultiCare Studie gebeten. 3317 Patienten meldeten sich zurück (Ausschöpfungsquote: 46,2 %), davon wurden weitere 128 Patienten, unter anderem auf Grund ihres vorzeitigen Todes, aus der Studie ausgeschlossen. Die finale Fallzahl der Studie belief sich auf 3189 Patienten, welche in standardisierten Interviews unter anderem zu Krankheiten, Arzneimitteln, Risikofaktoren, Gesundheits- und funktionellen Status und ihren soziodemographischen Daten befragt wurden.

Die Baseline Erhebung erfolgte von Juli 2008 bis November 2009 und es wurden drei Follow-Ups im Abstand von 15 Monaten durchgeführt. Für die folgenden Untersuchungen wurden jeweils die Baseline-Daten der MultiCare Studie verwendet. Die Studie wurde gemäß der Deklaration von Helsinki durchgeführt und ein positives Ethik Votum lag vor. Alle teilnehmenden Patienten haben eine Einverständniserklärung unterschrieben.

Weitere Details zur Datenerhebung und Studiendesign sind bei Schäfer et al. und in Publikation I zu finden [22,42].

1.3.2 Datenerfassung und Datenaufbereitung

Die verschreibungspflichtigen Arzneistoffe und die „over-the-counter“ (OTC) Arzneistoffe oder Substanzen wurden in einem „Brown-Bag“ Verfahren dokumentiert. Bei diesem Verfahren werden neben verschreibungspflichtigen Arzneistoffen, auch die OTC-Arzneistoffe und Substanzen aus dem Bereich der Selbstmedikation, die der Patient in den letzten drei Monaten eingenommen hat, erfasst. Auf diesem Wege wurden Informationen zu Produktnamen, Wirkstoff, Pharmazentralnummer, Darreichungsform, Dosis, Bedarfs-medikation oder regelmäßige Einnahme gewonnen. Die so erhobenen Arzneistoffe wurden analog des „Anatomical Chemical Classification“ (ATC) Systems von 2016 codiert, wobei Kombinationsarzneimittel vorher in die einzelnen Arzneistoffe aufgeteilt wurden. Die Einteilung in verschreibungspflichtige und OTC-Arzneistoffe erfolgte gemäß den Richtlinien des deutschen Arzneimittelgesetzes [43].

1.3.3 Explorative Faktorenanalyse und Korrelation der Arzneistofffaktoren mit den Morbiditätsclustern

Die deskriptiven Ergebnisse zur Anzahl der Arzneimittel pro Patient und Einteilung der Arzneimittel gemäß des ATC Systems in die einzelnen Untergruppen wurden mit Hilfe von Excel 2010 und 2016 (Microsoft Office 2010 und 2016, Redmond, USA) gewonnen.

Zur Generierung der Arzneistofffaktoren wurde eine explorative Faktorenanalyse mittels STATA 12.1 (StataCorp, College Station, USA) durchgeführt. Dafür wurden die pharmakologischen Untergruppen (ATC Level 3) verwendet, wobei nur ATC Level 3 Gruppen mit einer Prävalenz von mindestens 5 % mit in die Untersuchung einbezogen wurden. Die so gewonnenen Arzneistofffaktoren wurden mittels Spearman-Rank-Korrelation mit den bereits durch Schäfer et al. publizierten Morbiditätsclustern (CMD: „cardiovascular and metabolic disorder cluster“; ADS/P: „anxiety, depression, somatoform disorders and pain“ und NPS: „neuropsychiatric disorders“) assoziiert (Signifikanzniveau $p \leq 0{,}05$). Details zu den deskriptiven Analysen, der explorativen Faktorenanalyse, sowie der oben genannten Korrelation zwischen Arzneistofffaktoren und Morbiditätsclustern sind in Publikation I zu finden [42].

1.3.4 Klassifizierung gemäß PIM-Listen und Berechnung der Assoziation zwischen der PIM Einnahme und der kognitiven Funktion

Es wurden drei PIM Listen, die sowohl gut etabliert als auch in der Praxis gut für den Deutschen Verordnungsraum anwendbar sind, ausgewählt, um diese miteinander zu vergleichen: Die FORTA-Liste, die PRISCUS-Liste und die EU(7)-PIM-Liste.

Die FORTA-Liste (Fit fOr the Aged) (2018) umfasst 296 Arzneistoffe aus 30 Indikationsgruppen und teilt Arzneistoffe indikationsbezogen in A (absolute), B (beneficial), C (careful) und D (don't) ein. Die Kategorien A und B dienen dazu, eine eventuelle Unterversorgung aufzudecken. Arzneistoffe aus der Kategorien C und D weisen fragwürdige Sicherheit und therapeutische Effektivität auf und wurden somit als PIM klassifiziert [30].

Die PRISCUS-Liste (2010) ist eine etablierte Negativliste in Deutschland, die 83 Arzneistoffe aus 18 verschiedenen Indikationsgebieten umfasst. Die Arzneistoffe werden zum Teil dosisabhängig eingestuft und es werden Therapiealternativen aufgeführt [25].

Die EU(7)-PIM-Liste (2015) ist eine europäische Negativliste, welche 282 Arzneistoffe aus 34 Indikationsgebieten umfasst. Es werden zusätzlich Hinweise zu alternativen Arzneistoffen fund maximalen Tagesdosen der PIM gegeben [31].

FORTA unterscheidet im Gegensatz zu PRISCUS und EU(7)-PIM-Liste nicht zwischen Bedarfsmedikation oder einem regelmäßig eingenommenen Arzneistoff. Weiterhin klassifiziert FORTA, im Unterschied zu PRISUCUS und EU(7)-PIM-Liste, die Arzneistoffe dosisunabhängig. Um eine Vergleichbarkeit zwischen den drei Listen zu gewähren, wurde die Bedarfsmedikation in die Analysen mit einbezogen und die Arzneistoffe wurde mittels PRISCUS und EU(7)-PIM-Liste unabhängig von ihrer Dosis klassifiziert.

Zur Berechnung der Assoziation zwischen der PIM Einnahme (separat für jede PIM-Liste) und der kognitiven Funktion ermittelt mit dem „Letter Digit Substitution Test" (LDST) wurde eine multivariate lineare Regression mit STATA 12.1 durchgeführt (Signifikanzniveau $p \leq 0,05$).

Detaillierte Informationen zu der Verwendung der einzelnen PIM-Listen und der genauen Methodik der multivariaten linearen Regression sind in Publikation II zu finden [44].

1.3.5 Berechnung der anticholinergen Last und der Assoziation zwischen der anticholinergen Last und der kognitiven Funktion

Zur Berechnung der anticholinergen Last wurden zwei verschiedene Scores verwendet um diese miteinander zu vergleichen: Zum einen der bereits etablierte und validierte ADS-Score und zum anderen der speziell für den deutschen Arzneimittelmarkt entwickelte deutsche ACB-Score.

Der ADS-Score umfasst 413 Substanzen. Es erfolgt eine Einteilung in vier Kategorien. Ein ADS-Score von 0, entspricht keiner anticholinerge Last (296 Arzneistoffe), ein ADS-Score von 1 ist gleichzusetzen mit einer geringen anticholinergen Last (71 Arzneistoffe), ein ADS-Score von 2 beschreibt Arzneistoffe mit einer mittleren anticholinergen Last (12 Arzneistoffe) und ein ADS-Score von 3 umfasst die Arzneistoffe mit einer hohen anticholinergen Last (34 Arzneistoffe) [38].

Der deutsche ACB-Score bewertet 507 Substanzen welche in vier Kategorien eingeteilt werden. Ein ACB-Score von 0 ist gleichbedeutend mit keiner anticholinergen Last (356 Arzneistoffe), ein ACB-Score von 1 bedeutet eine geringe anticholinerge Last (104 Arzneistoffe), ein ACB-Score von 2 entspricht einer mittleren anticholinergen Last (18 Arzneistoffe) und ein ACB-Score von 3 bedeutet, es liegt eine hohe anticholinerge Last (34 Arzneistoffe) vor [41].

Anschließend wurden die Scores der Patienten jeweils separat für den ADS und den deutschen ACB-Score aufsummiert, um die individuelle anticholinerge Last eines Patienten je nach Score zu berechnen.

Auch hier wurde eine multivariate lineare Regression mit STATA 12.1 durchgeführt, um die Assoziation zwischen der individuellen anticholinergen Last und der kognitiven Funktion der Patienten, bestimmt mittels LDST, ermitteln zu können (Signifikanzniveau $p \leq 0,05$). Hierbei, wurden beide Scores separat untersucht.

Eine ausführliche Beschreibung der oben genannten Methoden findet sich in der Publikation III [45].

1.3.6 Subgruppenanalyse

Die folgenden Analysen wurden mit STATA 12.1 und SPSS 23/24 (IBM, Armonk, USA) durchgeführt. Die Subgruppenanalysen bezüglich des Einflusses von Alter (< 80 Jahre und

≥ 80 Jahre alt), Geschlecht und der Anzahl der Arzneistoffe (Median Split: 0 bis 7 Arzneistoffe und 8 bis 29 Arzneistoffe) auf die Anzahl der eingenommen PIM und die anticholinerge Last wurden mit einem zweiseitigen t-Tests durchgeführt. Der geschlechtsabhängige Gebrauch von OTC-Arzneistoffen wurde mittels Chi-Quadrat-Test untersucht. Zur Ermittlung der Abhängigkeit zwischen der Anzahl der eingenommenen Arzneistoffe und dem Geschlecht wurde ein Mann-Whitney-U-Test durchgeführt. Mittels Spearman-Rank-Korrelation wurde der Effekt des Alters der Patienten auf die Anzahl der eingenommenen Arzneistoffe ermittelt. Bei allen oben genannten Test wurde ein alpha-Level von 5 % ($p \leq 0,05$) als statistisch signifikant angesehen.

Auch hier finden sich in den Publikation I – III nähere Informationen zur Durchführung [42,44,45].

1.4 Ergebnisse

1.4.1 Charakterisierung des multimorbiden Patientenkollektives

Die 3189 Patienten waren zwischen 65 und 85 Jahre alt und nahmen zusammen 24.535 Arzneistoffe ein, wobei 875 unterschiedliche Substanzen gefunden wurden. 59,3 % der eingeschlossenen Patienten waren Frauen. Jeder Patient nahm durchschnittlich 7,7 (± 3,9) Arzneistoffe bei im Mittel 7,0 (± 2,0) diagnostizierten chronischen Erkrankungen ein (Median: 7 Arzneistoffe; Spannbreite: 0 bis 27 Arzneistoffe).

Die am häufigsten gefundenen verschreibungspflichtigen Arzneistoffe waren Simvastatin (34,9 %), Hydrochlorothiazid (34,7 %) und Ramipril (21,8 %). Die am häufigsten gefundenen OTC-Arzneistoffe oder Substanzen waren Acetylsalicylsäure als Thrombozyten-aggregationshemmer (35,6 %), Magnesium (24,0 %) und Kalzium (17,2 %). Insgesamt waren 24,2 % (5935) der ermittelten Arzneistoffe oder Substanzen aus dem OTC Bereich. Auf die anatomische Hauptgruppe des kardiovaskulären Systems (ATC C) entfielen die meisten Arzneistoffe mit 37,7 %, gefolgt von Arzneistoffe aus der Hauptgruppe Verdauungstrakt und Stoffwechsel (ATC A) mit 20,4 % und Arzneistoffe aus der Hauptgruppe Nervensystem (ATC N) mit 10,2 % (siehe Abbildung 1).

Table 1. Distribution of 24,535 drugs according to anatomical main group (ATC 1st level) and the top 20 ATC 5th level drugs (sorted according to their ATC 1st level) of 3189 patients of the MultiCare cohort and their proportion within the 1891 female patients in Germany (multiple use possible) (2008–2009).

ATC 1st level	ATC 5th level drugs	Frequency	Proportion per total number of drugs [%]	Proportion per patient [%]	Frequency for female (Proportion per female [%])
Cardiovascular system		9257	37.7		5162 (55.8%)
	Simvastatin	1114		34.9	526 (47.2%)
	Hydrochlorothiazide	1106		34.7	654 (59.1%)
	Ramipril	695		21.8	347 (49.9%)
	Metoprolol	661		20.7	375 (56.7%)
	Bisoprolol	629		19.7	368 (58.5%)
	Amlodipine	466		14.6	258 (55.4%)
	Torasemide	376		11.8	203 (54.0%)
	Enalapril	330		10.3	188 (57.0%)
	Lisinopril	216		6.8	109 (50.5%)
Alimentary tract and metabolism		5006	20.4		3286 (65.6%)
	Magnesium	765		24.0	541 (70.7%)
	Calcium	548		17.2	454 (82.8%)
	Omeprazole	448		14.0	278 (62.1%)
	Metformin	436		13.7	220 (50.5%)
	Cholecalciferol	392		12.3	337 (86.0%)
Nervous system		2507	10.2		1766 (70.4%)
Blood and blood forming organs		1904	7.8		955 (50.2%)
	Acetylsalicylic acid	1134		35.6	573 (50.5%)
	Phenprocoumon	441		13.8	215 (48.8%)
Musculo-skeletal system		1819	7.4		1186 (65.2%)
	Allopurinol	402		12.6	166 (41.3%)
	Diclofenac	390		12.2	268 (68.7%)
	Ibuprofen	335		10.5	244 (72.8%)
Respiratory system		1361	5.5		770 (56.6%)
Systemic hormonal preparations		999	4.1		773 (77.4%)
	Levothyroxine	616		19.3	504 (81.8%)
Genito-urinary system and sex hormones		568	2.3		241 (42.4 %)
Sensory organs		488	2.0		309 (63.3%)
Dermatologicals		190	0.8		123 (64.7%)
Antineoplastic and immunomodulating agents		154	0.6		122 (72.7%)
Various		106	0.4		67 (63.2%)
Antiinfectives		99	0.4		76 (76.8%)
Herbal and homeopathic agents		72	0.3		54 (75.0%)
Antiparasitic products		5	0.02		5 (100.0 %)

Abbildung 1: Verteilung der 24.535 Arzneistoffe gemäß der anatomischen Hauptgruppen des ATC Codes und die Top 20 Arzneistoffe der MultiCare Kohorte (3189 Patienten) [42]

Zwar konnte zwischen den Geschlechtern kein Unterschied in der Art der ermittelten Arzneistoffe gefunden werden, jedoch haben Frauen signifikant mehr Arzneistoffe eingenommen als Männer (7,9 ± 3,9 versus 7,4 ± 3,8 Arzneistoffe; $p = 0{,}002$). Außerdem nahmen Frauen signifikant mehr OTC-Arzneistoffe ein als Männer (26,8 % versus 20,1 %; $p < 0{,}001$). Zusätzlich konnte gezeigt werden, dass die Patienten mit steigendem Alter signifikant mehr Arzneistoffe einnahmen (65 bis 73,91 Jahre: 7,3 Arzneistoffe vs. 73,91 bis 85 Jahre: 8,1 Arzneistoffe). Dies war aber nur mit einer geringen Effektstärke zu beobachten ($\rho = 0{,}103$; $p > 0{,}001$).

1.4.2 Arzneistofffaktoren und deren Korrelation mit den Morbiditätsclustern

Es wurden vier Arzneistofffaktoren für Frauen und fünf Arzneistofffaktoren für Männer extrahiert.

Wie in Abbildung 2 dargestellt, konnten für die männliche Studienpopulation folgende fünf Faktoren gefunden werden: Arzneistoffe für chronisch obstruktive Lungenerkrankungen (D-OPD) (10,8 %; 140), (II) Arzneistoffe für koronare Herzkrankheiten und Hypertonie (D-CDH) (64,4 %; 836), (III) Arzneistoffe gegen Osteoporose (D-Osteo) (14,2 %; 184), (IV) Arzneistoffe für Herzinsuffizienz (D-HF) (5,6 %; 73) und (V) Arzneistoffe gegen Schmerzen (D-Pain) (12,7 %; 165). Abbildung 3 zeigt die Arzneistofffaktoren für die weibliche Studienpopulation: Arzneistoffe gegen Osteoporose (D-Osteo) (17,2 %; 326), (2)) Arzneistoffe für koronare Herzkrankheiten und Hypertonie (D-CDH) (22,7 %; 430), (3) Arzneistoffe für chronisch obstruktive Lungenerkrankungen (D-OPD) (9,0 %; 170) und (4) Diuretika und Arzneistoffe bei Gicht (D-DG) (9,9 %; 188).

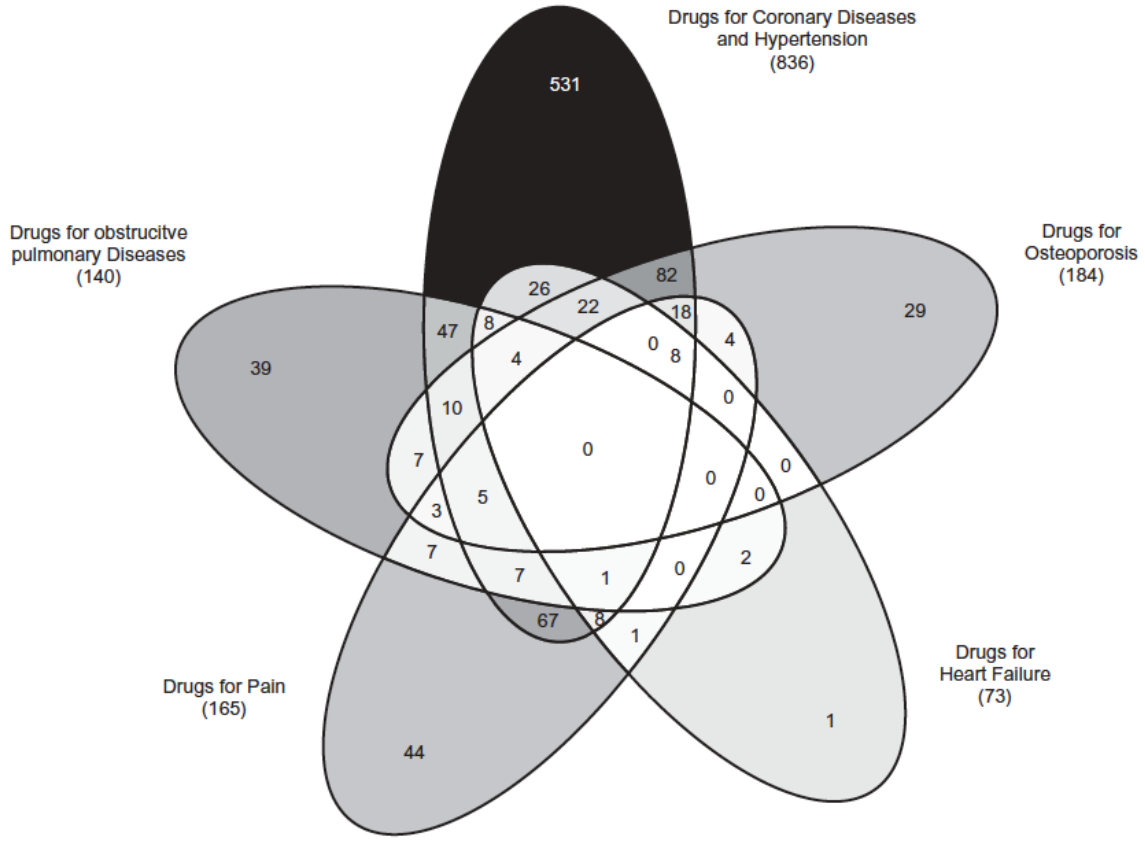

Figure 1. Overlapping of drug patterns (total number of patients) related to the total male population (1298) in Germany (2008–2009).

Abbildung 2: Überlappung der Arzneistofffaktoren der 1298 männlichen MultiCare Patienten und Darstellung der Patientenanzahl pro Faktor und pro Schnittmenge der einzelnen Faktoren [42]

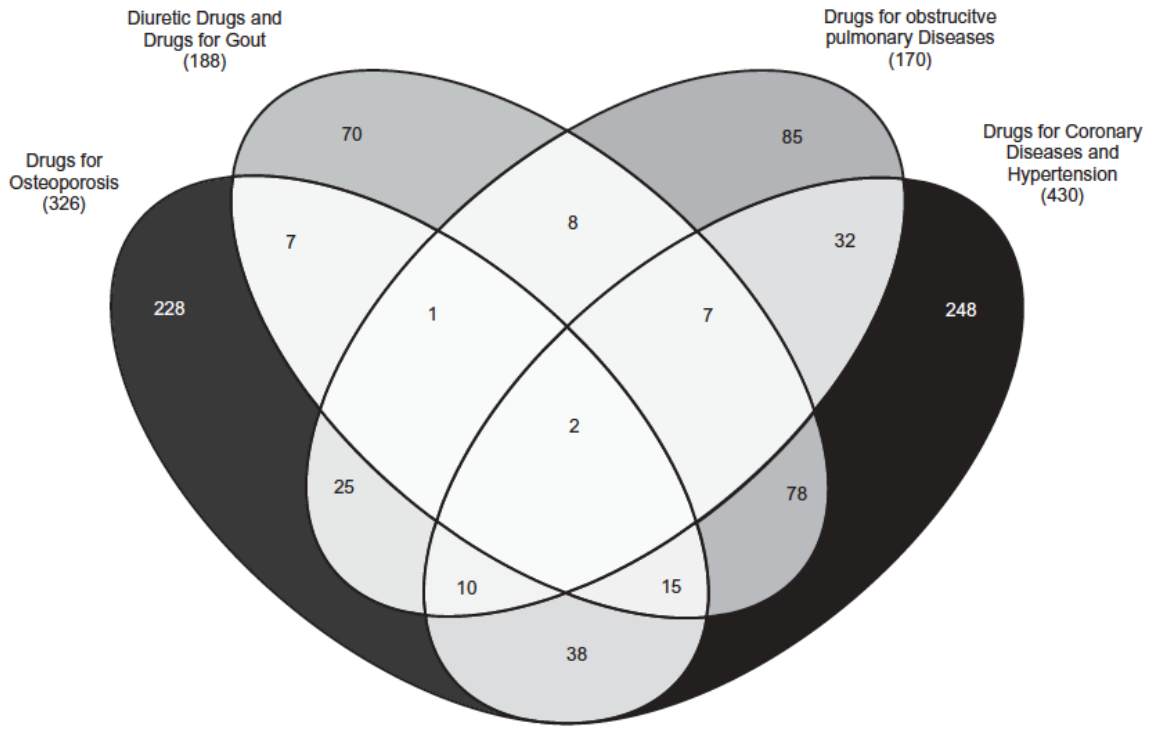

Figure 2. Overlapping of drug patterns (total number of patients) related to the total female population (1891) in Germany (2008–2009).

Abbildung 3: Überlappung der Arzneistofffaktoren der 1891 weiblichen MulitCare Patientinnen und Darstellung der Patientenanzahl pro Faktor und pro Schnittmenge der einzelnen Faktoren [42]

Mindestens einem der Faktoren konnten 75,0 % der Männer und 45,2 % der Frauen zugeordnet werden. Die kumulierte Häufigkeit für die Männer beträgt 35,4 % und für die Frauen 30,9 %. Dies drückt aus, wie groß der Anteil der Varianz der Arzneistoffe ist, welche durch das gewählte Faktoren-Modell erklärbar ist. Wie in Abbildung 2 und 3 zu erkennen ist, zeigten die einzelnen Faktoren zum Teil starke Überlappungen untereinander. Dementsprechend finden die Patienten sich in mehr als einem Faktor wieder. Insgesamt wurde festgestellt, dass 33,8 % (329) der Männer und 26,1 % (223) der Frauen mehr als einem Arzneistofffaktor zuzuordnen waren.

Die extrahierten Arzneistofffaktoren zeigten eine signifikante Korrelation mit ihren korrespondieren Morbiditätsclustern für beide Geschlechtergruppen. Mit einer mittleren Effektstärke war sowohl bei den Männern als auch bei den Frauen eine Assoziation zwischen dem CMD Cluster und dem D-CDH Faktor zu erkennen (männlich: $\rho = 0.376$, $p < 0.001$, CI 0.322 – 0.430, weiblich: $\rho = 0.301$, $p < 0.001$; CI 0.624 – 0.340). Alle weiteren signifikanten Korrelationen sind nur mit einer geringen Effektstärke aufgetreten ($\rho < 0.3$).

Detaillierte Information zu der Überlappung der Arzneistofffaktoren und deren genaue Zusammensetzung sowie zu den Korrelationen mit den Morbiditätsclustern sind in Publikation I zu finden [42].

1.4.3 Klassifizierung der potentiell inadäquaten Medikation und deren Assoziation mit der kognitiven Funktion

Insgesamt konnte bei 55,9 % der Patienten ein FORTA-PIM gefunden werden. Im Durchschnitt haben die Patienten 0,9 (± 1,0) FORTA-PIM pro Patient eingenommen und es wurden 11,6 % (2852) der Arzneistoffe als FORTA-PIM kategorisiert. Die häufigsten PIM gemäß FORTA waren Phenprocoumon (Kategorie C; 441 Patienten, 13,8 %), Produkte die Ginkgo Biloba Blätter Extrakt enthalten (Kategorie C, 152, 4,8 %) und Glimepirid (Kategorie C, 144, 4,5 %).

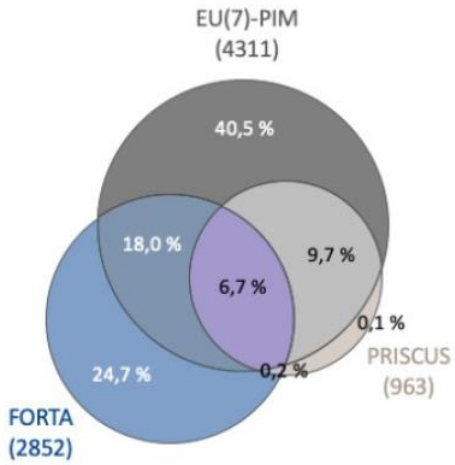

Figure 1 Venn diagram showing the overlap between FORTA, PRISCUS and EU(7)-PIM lists in terms of PIM (percentages sum up to 100%). FORTA, Fit fOR The Aged; PIM, potentially inappropriate medication.

Abbildung 4: Im Venn-Diagramm sind die Überlappungen zwischen FORTA, PRISCUS und EU(7)-PIM in Bezug auf die Anzahl der detektierten PIM pro PIM Liste dargestellt (die Prozente summieren sich auf zu 100 %) [44]

PRISCUS-PIM konnten bei 24,7 % der Patienten gefunden werden. Insgesamt wurden 3,9 % (963) der Arzneistoffe als PRISCUS-PIM klassifiziert und jeder Patient nahm im Mittel 0,3 (± 0,6) PRISCUS-PIM ein. Die häufigsten PRISCUS-PIM waren Amitriptylin (88 Patienten, 2,8 %), Acetyldigoxin (60, 1,9 %) und Nifedipin (53, 1,7 %).

Bei 70,1 % der Patienten konnte ein EU(7)-PIM gefunden werden. Im Mittel nahmen die Patienten 1,4 (± 1,3) EU(7)-PIM ein und es wurden 17,6 % (4311) der Arzneistoffe als EU(7)-PIM kategorisiert. Die häufigsten EU(7)-PIM waren Omeprazol (448 Patienten, 14,0 %), Diclofenac (390, 12,2 %) und Ibuprofen (335, 10,5 %).

Table 6 Multivariate linear regression model—impact of FORTA or PRISCUS or EU(7)-PIM use on cognitive function measured by LDST

LDST	Correlation coefficient	P value	95% CI
FORTA PIM per patient	−0.397	0.002	−0.644 to −0.150
Age	−0.340	<0.001	−0.383 to −0.296
Sex	2.538	<0.001	2.072 to 3.004
CASMIN3_2	2.348	<0.001	1.813 to 2.883
CASMIN3_3	3.791	<0.001	3.007 to 4.575
Income	2.407	<0.001	1.869 to 2.945
Number of diseases weighted by severity	−0.121	<0.001	−0.169 to −0.072
Number of taken drugs	−0.034	0.340	−0.105 to 0.036
PRISCUS PIM per patient	−0.464	0.025	−0.870 to −0.058
Age	−0.340	<0.001	−0.383 to −0.296
Sex	2.560	<0.001	2.093 to 3.026
CASMIN3_2	2.366	<0.001	1.831 to 2.901
CASMIN3_3	3.776	<0.001	2.992 to 4.561
Income	2.423	<0.001	1.885 to 2.961
Number of diseases weighted by severity	−0.127	<0.001	−0.176 to −0.079
Number of taken drugs	−0.060	0.079	−0.127 to 0.007
EU(7)-PIM per patient	−0.300	0.005	−0.508 to −0.092
Age	−0.344	<0.001	−0.387 to −0.300
Sex	2.597	<0.001	2.130 to 3.065
CASMIN3_2	2.351	<0.001	1.815 to 2.886
CASMIN3_3	3.772	<0.001	2.998 to 4.556
Income	2.409	<0.001	1.871 to 2.947
Number of diseases weighted by severity	−0.127	<0.001	−0.176 to −0.079
Number of taken drugs	−0.025	0.507	−0.101 to 0.050

Dependent variable: results from LDST; *independent variables*: FORTA PIM or PRISCUS PIM or EU(7)-PIM; *covariables* included in the regression model: sex, age, education standard (casmin3_2: comparison between medium and low educational standard; casmin3_3: comparison between high and low educational standard), number of diseases weighted by severity, income and number of taken drugs. Every PIM list is analysed separately in the same regression model.
FORTA, Fit fOR The Aged; LDST, letter digit substitution test; PIM, potentially inappropriate medication.

Abbildung 5: Multivariate lineares Regressionsmodel – Einfluss von FORTA-, PRISCUS- oder EU(7)-PIM-Gebrauch auf die kognitive Funktion ermittelt anhand des „Letter Digit Substitution Test“. Jede PIM Liste wurde separat im Modell berechnet.

Abhängige Variable: Ergebnisse aus dem „Letter Digit Substitution Test” (LDST); *unabhängige Variablen*: FORTA-PIM oder PRISCUS-PIM oder EU(7)-PIM; *Co-Variablen* welche in das Regressionsmodell mit eingeschlossen wurden: Geschlecht, Alter, Bildungsstandard (casmin3_2: Vergleich zwischen mittlerem und niedrigem Bildungsstandard; casmin3_3: Vergleich zwischen hohem und niedrigem Bildungsstandard), Krankheitsschwere, Einkommen, Anzahl der eingenommen Arzneistoffe pro Patient [44]

Abbildung 4 zeigt die Schnittmengen der drei PIM Listen, wobei zu erkennen ist, dass es nur kleine Schnittmenge zwischen allen drei PIM-Listen gibt. Im Gegensatz dazu findet sich die PRISCUS-Liste beinahe komplett in der EU(7)-PIM-Liste wieder.

Mittels multivariater linearer Regression konnte festgestellt werden, dass Patienten, die PIM angewendet haben, signifikant schlechtere Ergebnisse im LDST aufwiesen als Patienten, die weniger oder keine PIM anwandten. Wie in Abbildung 5 dargestellt, war dieser Effekt für jede der drei PIM-Listen zu beobachten (FORTA-PIM: -0,397; CI -0,644 – -0,150; p = 0,002; PRISCUS: -0,464; CI -0,870 – -0,058; p = 0,025 und EU(7)-PIM: -0,300; CI -0,508 – -0,092; p = 0,005). Zusätzlich wurde festgestellt, dass die FORTA Liste, verglichen mit der PRISCUS und der EU(7)-PIM-Liste, einen stärkeren negativen Effekt auf die kognitive Funktion der multimorbiden älteren Patienten hat (FORTA: -0,306; CI -0,567 – -0,044; p = 0,022; PRISCUS: –0,118; CI -0,652 – 0,276; p = 0,428 und EU(7)-PIM: -0,188; CI -0,416 – 0,072; p = 0,168).

Die ausführliche Beschreibung der Ergebnisse findet sich in Publikation II [44].

1.4.4 Anticholinerge Last und deren Assoziation mit der kognitiven Funktion

Es wurden 1764 Arzneistoffe als Anticholinergika mittels des ADS-Score klassifiziert. Bei 38,4 % (1226) aller Patienten trat mindestens ein ADS-Anticholinergikum auf. Im Mittel hatten die Patienten einen ADS-Score von 0,8 (± 1,27), und 10,5 % aller Patienten hatten einen ADS-Score von drei oder höher. Das häufigste Anticholinergikum mit einem niedrigen anticholinergen Potential laut ADS-Score war Furosemid (5,8 %, 185), das häufigste Anticholinergikum mit einem hohen Potential war Amitriptylin (2,8 %, 88). Die größten anatomischen Hauptgruppen hinsichtlich des ADS-Scores bildeten die Arzneistoffe aus dem kardiovaskulären System (ATC C) mit 36,6 % (646) und dem zentralen Nervensystem (ATC N) mit 31,9 % (563).

Mittels des deutschen ACB-Score konnten 2750 Arzneistoffe als Anticholinergika oder Arzneistoffe mit anticholinergem Risiko identifiziert werden. Insgesamt konnte bei 53,7 % (1714) der Patienten mindestens ein Arzneistoff mit anticholinergem Risiko gefunden. Im Mittel hatten die Patienten einen deutschen ACB-Score von 1,2 (± 1,6) und 18,1 % (567) aller Patienten der MultiCare Studie hatten eine ACB-Score von drei oder höher. Metformin war mit 13,7 % (436) der Arzneistoff mit geringem anticholinergen Potential, der am häufigsten eingenommen wurde, Tramadol (3,3 %; 105) der häufigste mit mittlerem anticholinergem Potential und Amitriptylin mit 2,8 % (88) der häufigste Arzneistoff mit hohem anticholinergen Potential. Die meisten als Anticholinergika klassifizierten Arzneistoffe gemäß des deutschen

ACB-Scores stammten mit 29,5 % (812) aus der anatomischen Hauptgruppe des zentralen Nervensystems (ATC N), gefolgt von Arzneistoffen des kardiovaskulären Systems (ATC C) mit 25,7 % (709).

Table 5 The two linear regression models for the association between cognitive function (LDST) and anticholinergic score according to anticholinergic drugs scale (ADS) score (significant p values are marked in bold)

LDST	Regression coefficient	P value	95% CI
ADS score per patient	−0.37	**<0.001**	−0.55 to −0.2
Sex	−0.34	**<0.001**	−0.38 to −0.3
Age	2.57	**<0.001**	2.11 to 3.04
Casmin3_2	2.33	**<0.001**	1.8 to 2.87
Casmin3_3	3.68	**<0.001**	2.91 to 4.45
Income	2.45	**<0.001**	1.92 to 2.98
Number of diseases weighted by severity	−0.13	**<0.001**	−0.18 to −0.09
ADS score per patient	−0.26	**0.008**	−0.46 to −0.07
Sex	−0.34	**<0.001**	−0.38 to −0.3
Age	2.58	**<0.001**	2.12 to 3.04
Casmin3_2	2.32	**<0.001**	1.79 to 2.85
Casmin3_3	3.71	**<0.001**	2.94 to 4.48
Income	2.44	**<0.001**	1.91 to 2.97
Number of diseases weighted by severity	−0.12	**<0.001**	−0.16 to −0.07
FORTA PIM	−0.35	**0.005**	−0.59 to −0.11

Dependent variable: results from LDST; independent variable: ADS score; covariables included in the regression model: sex, age, education standard (casmin3_2: comparison between medium and low educational standard; casmin3_3: comparison between high and low educational standard), income, number of diseases weight by severity, used FORTA drugs.
ACB, anticholinergic burden; FORTA, Fit for the Aged; LDST, letter digit substitution test.

Table 6 The two linear regression models for the association between cognitive function (LDST) and anticholinergic score according to the German anticholinergic burden (ACB) score (significant p values are marked in bold)

LDST	Regression coefficient	P value	95% CI
ACB score per patient	−0.33	**<0.001**	−0.47 to −0.19
Sex	−0.34	**<0.001**	−0.39 to −0.3
Age	2.60	**<0.001**	2.14 to 3.06
Casmin3_2	2.33	**<0.001**	1.8 to 2.86
Casmin3_3	3.68	**<0.001**	2.9 to 4.45
Income	2.42	**<0.001**	1.89 to 2.95
Number of diseases weighted by severity	−0.13	**<0.001**	−0,17 to −0,08
ACB score per patient	−0.24	**0.003**	−0.40 to −0.08
Sex	−0.34	**<0.001**	−0.39 to −0.30
Age	2.60	**<0.001**	2.13 to 3.06
Casmin3_2	2.32	**<0.001**	1.79 to 2.85
Casmin3_3	3.70	**<0.001**	2.93 to 4.47
Income	2.42	**<0.001**	1.89 to 2.95
Number of diseases weighted by severity	−0.12	**<0.001**	−0.17 to −0.07
FORTA PIM per patient	−0.29	**0.030**	−0.54 to −0.03

Dependent variable: results from LDST; independent variable: ACB score; covariables included in the regression model: sex, age, education standard (casmin3_2: comparison between medium and low educational standard; casmin3_3: comparison between high and low educational standard), income, number of diseases weight by severity, used FORTA drugs.
.FORTA, Fit for the Aged; LDST, letter digit substitution test.

Abbildung 6: Darstellung der zwei Regressions-Modelle, welche die Assoziation zwischen kognitiver Funktion mittels LDST und der anticholinergen Last mittels ADS beziehungsweise des deutschen ACB-Score veranschaulichen

Abhängige Variable: Ergebnisse aus dem LDST; *Unabhängige Variable*: ADS-Score/ACB-Score; *Co-Variablen* die in das Regressionsmodell mit eingeschlossen wurden: Geschlecht, Alter, Bildungsstandard (casmin3_2: Vergleich zwischen mittlerem und niedrigem Bildungsstandard; casmin3_3: Vergleich zwischen hohem und niedrigem Bildungsstandard), Einkommen, Krankheitsschwere, FORTA-PIM [45]

Es konnte festgestellt werden, dass 80,2 % der ADS und 73,4 % der deutschen ACB Anticholinergika ein geringes anticholinerges Potential aufwiesen.

Abbildung 6 zeigt die zwei Regressions-Modelle, welche entwickelt wurden, um den Einfluss der Anticholinergika-Einnahme auf die kognitive Funktion gemäß dem LDST bestimmen zu können. Das erste Modell wurde für Alter, Geschlecht, Einkommen, Bildungsstandard und Schwere der Krankheiten adjustiert. Im zweiten Modell wurde zusätzlich die Anzahl an potentiell inadäquaten Arzneimitteln nach FORTA pro Patient mit aufgenommen. Modell 1 zeigt für beide Listen eine signifikante Reduktion der Leistungen im LDST (ADS: -0,37; $p \leq 0{,}001$ und ACB: -0,33; $p \leq 0{,}001$). Im zweiten Modell nimmt der Regressionskoeffizient durch die Hinzunahme der FORTA-PIM ab. Jedoch sieht man auch hier für beide Scores eine signifikante Abnahme der Leistung im LDST (ADS: -0,26; $p = 0{,}008$ und ACB: -0,24; $p = 0{,}003$).
Detaillierte Informationen zu den Ergebnissen der linearen Regressionen und der deskriptiven Ergebnisse sowie die Ergebnisse zu den Subgruppenanalysen befinden sich in Publikation III [45].

1.5 Schlussfolgerung und Diskussion

In der vorliegenden Arbeit erfolgte eine Charakterisierung der verschreibungspflichtigen und der nicht-verschreibungspflichtigen Arzneistoffe von multimorbiden, älteren Patienten hinsichtlich Verordnungsmustern, Einnahme von potentiell inadäquater Medikation und Anticholinergika sowie deren Einfluss auf die kognitive Funktion. Das Ziel bestand darin, neue Erkenntnisse zur Verbesserung der Arzneimitteltherapiesicherheit dieser vulnerablen Patientengruppe zu gewinnen und neue Informationen zur Optimierung der Therapie von multimorbiden, älteren Patienten zu generieren.

1.5.1 Arzneistofffaktoren und Einfluss von Multimedikation

Im Gegensatz zu bisherigen Studien wurden in die Analyse wurden die Daten der MultiCare Studie neben verschreibungspflichtigen auch nicht verschreibungspflichtige Arzneistoffe eingeschlossen. So konnten neue Erkenntnisse generiert werden, die große Relevanz bei der Verbesserung der Arzneimitteltherapiesicherheit älterer Patienten aufweisen: Annähernd ein Viertel der gefundenen Arzneistoffe innerhalb des Patientenkollektives waren OTC-Arzneistoffe, was wiederum die vergleichsweise höhere Rate an Arzneistoffen pro Patient erklärt [12,46]. Die höhere Anzahl an Arzneistoffen pro Patient weist auf Multimedikation im Alter hin. Zusätzlich wurde noch einmal verdeutlicht, dass multimorbide ältere Frauen mehr

OTC-Arzneistoffe und auch insgesamt mehr Arzneistoffe einnehmen als multimorbide ältere Männer. Eine mögliche Erklärung für eine höhere Anzahl an Arzneistoffe und speziell OTC-Arzneistoffen bei Frauen ist, dass Frauen häufig ein größeres Gesundheitsbewusstsein aufweisen als Männer [47].

Die ermittelten unterschiedlichen und nicht-zufälligen Arzneistofffaktoren umfassen Arzneistoffe aus unterschiedlichen pharmakologischen Arzneistoffgruppen. Viele der gefundenen Muster in den Verordnungen waren erwartbar, wie zum Beispiel die Zusammensetzung des D-CDH Faktors. Die starke Überschneidung der einzelnen Arzneistofffaktoren ist ein Hinweis auf Multimedikation. Darüber hinaus konnte Multimedikation an einem scheinbar gesünderen Patientenkollektiv sichtbar gemacht werden, da Patienten aus Pflegeheimen und Patienten mit Demenz nicht in das Studienkollektiv eingeschlossen wurden.

Calderón-Larrañaga et al. haben ähnliche Muster bei den verschreibungspflichtigen Arzneistoffen entdeckt. In der hier vorliegenden Studie wurden nun zusätzlich auch OTC-Arzneistoffe erfasst, sodass ein umfassenderer Einblick in den Arzneimittelgebrauch der multimorbiden, älteren Patienten möglich war [46]. Menditto et al. zeigten ähnliche Ergebnisse zu Multimorbiditäts- und Multimedikationsclustern, jedoch wurden in dieser Studie alle Patienten die älter als 65 Jahre alt waren aufgrund von Multikollinearität ausgeschlossen [48].

Weiterhin wurden die im Rahmen dieser Arbeit gefundenen Arzneistofffaktoren mit den bereits durch Schäfer et al. publizierten Morbiditätsclustern derselben Kohorte verglichen [23]. Es wurde bestätigt, dass eine Assoziation zwischen den Morbiditätsclustern und ihren korrespondierenden Arzneistofffaktoren besteht. Auch wenn dies nur mit einer geringen Effektstärke gezeigt werden konnte, sind die gefundenen Zusammenhänge nicht zufällig. Es konnte so gezeigt werden, dass die multimorbiden, älteren Patienten entsprechend ihrer diagnostizierten chronischen Erkrankungen therapiert werden.

1.5.2 Potentiell inadäquate Medikation und dessen Einfluss auf die kognitive Funktion

Mittels der drei PIM-Listen – FORTA, PRISCUS und EU(7)-PIM-Liste – wurden sehr unterschiedliche Prävalenzen an potentiell inadäquater Medikation innerhalb der Gruppe der multimorbiden älteren Patienten dokumentiert, was sich mit Ergebnissen aus der Literatur deckt [49–52]. Mit der PRISCUS-Liste wurden eher „ältere“ und „klassische“ Arzneistoffe, wie

zum Beispiel Antidepressiva, Hypnotika und Sedativa als PIM klassifiziert. Darüber hinaus umfassen die EU(7)-PIM-Liste und FORTA-Liste hingegen noch weitere Arzneistoffe. So detektierte die EU(7)-PIM-Liste Protonenpumpeninhibitoren (PPI) und nichtsteroidale Antiphlogistika (NSAID) als die häufigsten PIM. Die FORTA-Liste stuft zusätzlich Arzneistoffe oder Substanzen ohne bewiesen Nutzen und Effektivität als PIM ein. Dies erklärt, warum mittels FORTA- und EU(7)-PIM-Liste höhere Prävalenzen an potentiell inadäquater Medikation gefunden worden sind als mit der PRISCUS-Liste.

Auch wenn die PRISCUS-Liste sich nahezu in der EU(7)-PIM-Liste wiederfindet, wiesen die PIM-Listen zum Teil nur geringe Schnittmengen untereinander auf und die detektieren PIM zeigten eine breite Heterogenität. Es ist fraglich, ob es für eine adäquate Identifizierung von PIM ausreichend ist, nur eine Liste zu verwenden, da der Fokus der einzelnen PIM-Listen unterschiedlich ist. Das Medikationsmanagement für ältere, multimorbide Patienten ist ein sehr komplexer Prozess, da nur limitierte Daten aus klinischen Studien verfügbar sind. Obwohl man mit einer Liste höchstwahrscheinlich nicht alle PIM erfassen wird, ist es dennoch wichtig, PIM zu identifizieren [24].

Wie in anderen Studien ebenfalls gezeigt, zeigen Frauen neben einer erhöhten Wahrscheinlichkeit für Multimedikation auch eine erhöhte Wahrscheinlichkeit für die Einnahme von als PIM eingestuften Arzneistoffen [49,53]. In einer Studie gab es Hinweise darauf, das für Frauen insbesondere aufgrund eines gesteigerten Gesundheitsbewusstsein im Vergleich zu männlichen Patienten eine erhöhte Wahrscheinlichkeit besteht eine Depression diagnostiziert zu bekommen und somit mehr Antidepressiva, Analgetika und Sedativa einzunehmen [52].

Es konnte gezeigt werden, dass die Einnahme von PIM zu schlechteren Leistungen im LDST führte, was auf eine Verschlechterung der kognitiven Funktion der Patienten hindeutete. Muhlack et al. konnte ebenfalls starke kognitive Einschränkungen der Patienten bei Einnahme von PIM gemäß der PRISCUS-Liste, der EU(7)-PIM-Liste oder der Beers-Liste feststellen [49]. Darüber hinaus wurden in den meisten anderen Studien, die sich mit ähnlichen Fragestellungen beschäftigt haben, entweder speziell Patienten mit Demenz untersucht oder diese nicht explizit ausgeschlossen [54,55]. Da eine Demenzerkrankung nicht standardisiert von den Hausärzten bewertet und diagnostiziert werden konnte, kann eine kognitive Einschränkung der Patienten zu Beginn der Datenerfassung nicht ausgeschlossen werden. Dennoch wurde mittels der Daten der MultiCare Studie gezeigt, dass in einem vermeintlich

gesünderen Patientenkollektiv kognitive Einschränkungen unter PIM-Gebrauch auftraten, da Demenz ein Ausschlusskriterium darstellte. Die FORTA-Liste konnte die verminderte kognitive Funktion am besten erklären. Dies könnte sich dadurch erklären lassen, dass die FORTA-Liste im Gegensatz zur PRISCUS und EU(7)-PIM-Liste ein implizites Tool darstellt und die Arzneistoffe indikationsbasiert bewertet. Zudem ist es die aktuellste der drei beschriebenen Listen (letztes Update 2018) [56].

1.5.3 Anticholinerge Last und deren Einfluss auf die kognitive Funktion

Der ADS und der deutsche ACB-Score lieferten vergleichbare Ergebnisse hinsichtlich der ermittelten Scores, welche auch gut im Einklang mit der beschriebenen Literatur sind [57–60]. Für die Einnahme von Anticholinergika wurde Multimedikation als Risikofaktor identifiziert [61,62]. Als ein weiterer Risikofaktor wurde das Geschlecht identifiziert: Frauen haben ein erhöhtes Risiko, anticholinerge Substanzen einzunehmen, was sowohl mit einem erhöhten Gesundheitsbewusstsein, als auch einer erhöhten Rate an diagnostizierten Depressionen begründet werden kann [63]. Gerade Arzneistoffe der ATC Gruppe des zentralen Nervensystem stellen eine der größten Gruppen dar, die Einfluss auf die anticholinerge Last haben. Zusätzlich konnte festgestellt werden, dass insbesondere Arzneistoffe mit einer geringen anticholinergen Last (Score von 1) und vor allem Arzneistoffe aus dem kardiovaskulären System in hohem Maß zur individuellen anticholinergen Last der multimorbiden älteren Patienten beitragen, da vor allem diese in den Top 10 des ADS und deutschen ACB-Scores vorhanden waren. Das multimorbide ältere Patienten eine Vielzahl von Arzneistoffen aus dem Bereich der kardiovaskulär wirksamen Arzneistoffe verordnet bekommen, die gleichzeitig eine niedrige anticholinerge Last aufweisen ist auch bereits in der Literatur beschrieben [64]. Andere Studien weisen auf die Gefahr von Substanzen mit niedriger anticholinerger Last hin und zeigen auf, dass diese zu kumulativen anticholinergen Effekten führen [64,65]. In der Literatur ist beschrieben, dass kumulative anticholinerge Effekte zu vermehrten Krankenhausaufenthalten und einer erhöhten Mortalität führen [66–68].

Mittels multivariater linearer Regression wurde festgestellt, dass eine hohe anticholinerge Last gemäß ADS und deutschem ACB-Score mit einer verminderten kognitiven Funktion gemäß LDST-Test einhergeht. Die Ergebnisse zum Einfluss der Anticholinergika-Einnahme und deren Einfluss auf die kognitive Funktion wurden bisher in der Literatur nicht eindeutig

beschrieben [60,67,69]. Die individuell variierenden cholinergen Reserven im zentralen Nervensystem führen zu einer individuellen Sensitivität gegenüber zentralen anticholinergen Effekten [70]. Weiterhin wurden zum Teil sehr unterschiedliche Scores verwendet um die Medikation der Patienten zu bewerten. Im Gegensatz zur MultiCare Studie untersuchten die meisten Studien speziell Patienten mit Demenz oder schlossen Patienten mit demenziellen Erkrankungen ein [71]. So konnte anhand der vorliegenden Ergebnisse gezeigt werden, dass bei einem vermeintlich gesünderen Patientenkollektiv negative Effekte auf die kognitive Funktion mit der Einnahme von Anticholinergika assoziiert werden können. Weiterhin konnte gezeigt werden, dass eine alleinige Analyse der Medikation hinsichtlich Anticholinergika oder PIM nicht ausreichend ist, da durch die Hinzunahme von FORTA-PIM als Co-Variable mit in das Regressionsmodell eine Abnahme der Leistung im LDST um ein Zehntel zu beobachten war.
Abschließend ließ sich feststellen, dass mit Hilfe der Untersuchungen gezeigt werden konnte, dass die Einnahme von Anticholinergika gemäß ADS und deutschem ACB-Score einen negativen Einfluss auf die kognitiven Fähigkeiten der Patienten hat [60,67,69].

1.5.4 Methodische Stärken und Schwächen der Arbeit

Auf Grund der großen Anzahl an eingeschlossenen Patienten (3189) und den mit Bedacht ausgewählten Ein- und Ausschlusskriterien, wurde ein gut selektiertes Patientenkollektiv für die multimorbide, ältere Gesellschaft in Deutschland ausgewählt. Insbesondere der Ausschluss von Patienten, die in Alten- und Pflegeheimen leben, führt dazu, dass die MultiCare Kohorte ein im Schnitt gesünderes Patientenkollektiv aufweist als andere Studien. Dies hat sich als Stärke dieser Studie manifestiert, da so Probleme in der Arzneimitteltherapie in einem vermeintlich noch gesünderen Patientenkollektiv beobachtet und bewertet werden konnten. Eine weitere Stärke dieser Studie ist, dass neben verschreibungspflichtigen Arzneistoffen auch nicht verschreibungspflichtige Arzneistoffe und Substanzen im Rahmen des „Brown-Bag“ Verfahren mit erhoben wurden. Viele epidemiologische Studien mit entsprechend hohen Patientenzahlen zu multimorbiden älteren Patienten berufen sich auf Krankenkassendaten, welche OTC-Arzneistoffe und Substanzen nicht miterfassen konnten.
Das „Brown-Bag“-Verfahren wies jedoch auch methodische Nachteile auf. Zum Einen konnte keine Aussage über die Adhärenz getroffen werden, zum Anderen konnte nicht konsequent eine Tagesdosis und Wirkstärke für die Arzneistoffe dokumentiert werden, wodurch es nicht möglich war, die Arzneistoffe hinsichtlich ihrer Tagesdosis gemäß EU(7)-PIM-Liste und

PRISCUS-Liste zu kategorisieren. Deshalb ist es möglich, dass der PIM Gebrauch gemäß EU(7)-PIM-Liste und PRISCUS-Liste leicht überschätzt ist. Andererseits wurden die FORTA-PIM rein indikationsbezogen analysiert, wodurch es möglich ist, dass der FORTA-PIM Gebrauch bei den älteren multimorbiden Patienten sogar unterschätzt wurde. Die Bedarfsmedikation wurde in die Analysen mit einbezogen. Zum Einen, da FORTA hinsichtlich Bedarf und täglichem Gebrauch keinen Unterschied macht, zum Anderen, da gerade kritische Arzneistoffe wie NSAIDs, PPI oder Benzodiazepine nicht unterschätzt werden sollten, weil die Patienten im Rahmen des „Brown-Bag"-Verfahrens selbst Auskunft über die Einnahme der Arzneistoffe gegeben haben.

Auch wenn auf Grund der acht ausgewählten Studienzentren regionale Verschreibungseffekte nicht komplett ausgeschlossen werden können, wurde durch die Auswahl der statistischen Methoden angestrebt, diese Effekte zu minimieren. Im Fall der explorativen Faktorenanalyse wurde anstatt der Einzelsubstanz eine Analyse auf Ebene der pharmakologische Subgruppe (ATC Level 3) durchgeführt. Bei den multivariaten linearen Regressionen zur Berechnung der Assoziation zwischen PIM-Einnahme beziehungsweise Anticholinergika-Gebrauch und der kognitiven Funktion wurde mit einem Mehrebenenmodell gerechnet, um für die Verschreibungseffekte der einzelnen Zentren und Hausärzte zu adjustieren. Die kognitive Funktion wurde mittels „Letter Digit Substitution Test" bestimmt. Kognitive Einschränkungen sind ein sehr komplexes Krankheitsbild und der LDST zeigt nur einen Aspekt der kognitiven Funktion des Patienten auf. Da aber in der Literatur beschrieben ist, dass Alter, Geschlecht und der Bildungsstandard einen Einfluss auf die Ergebnisse im LDST haben wurde diese Variablen neben anderen Variablen mit in die Modelle einbezogen [72,73]. Zusätzlich wurden fehlende Werte mittels „Hot-Deck-Imputation" ersetzt, um einen Bias zu vermeiden, der sonst durch umfassenden Ausschluss von Patienten aufgrund fehlender Werte entstehen würde [23].

1.5.5 Implikationen für weitere Forschungen

Weitere Studien könnten sich mit der Auswertung der Follow-Up-Daten der MultiCare Studie beschäftigen, um auch longitudinale Effekte, speziell hinsichtlich des Gebrauchs der potentiell inadäquaten Medikation und dem Anticholinergika-Gebrauch und deren Einfluss auf die kognitiven Fähigkeiten, zu beobachten. Ein weiterer interessanter Ansatz sind Untersuchungen zum „Deprescribing" bei multimorbiden älteren Patienten. Speziell sollte die

Auswirkung der Reduktion von Anticholinergika und potentiell inadäquater Medikation bei multimorbiden älteren Patienten auf die kognitive Funktion über einen längeren Zeitraum analysiert werden. Wichtig hierbei ist, dass ein valider Prozess entwickelt wird, der von einem multidisziplinären Team betreut und überwacht wird.
Auch eine Überarbeitung und Vereinheitlichung der publizierten Listen zur Identifizierung von potentiell inadäquater Medikation im Alter, zur Verbesserung der Nutzbarkeit dieser Listen im klinischen Alltag und der hausärztlichen Versorgung, wären ein guter Ansatz für weitere Arbeiten.

1.5.6 Implikationen für die Arzneimitteltherapiesicherheit und die Versorgungspraxis

Im Rahmen dieser Promotionsarbeit konnte gezeigt werden, dass die Arzneimitteltherapie von multimorbiden, älteren Patienten sehr vielschichtig und anspruchsvoll ist. Die drei durchgeführten Untersuchungen beleuchten die Arzneimitteltherapie dieser Patienten auf verschiedenen Ebenen, zeigen Risiken auf und liefern Informationen und Tools, um die Arzneimitteltherapie und Arzneimitteltherapiesicherheit der multimorbiden älteren Patienten zu verbessern. Durch das Identifizieren der Arzneistofffaktoren konnten Muster innerhalb der Verordnungen und der OTC-Arzneistoffe aufgedeckt werden und so war eine Charakterisierung des Patientenkollektives möglich. Gleichzeitig wurde durch die Überschneidungen zwischen den einzelnen Faktoren dargelegt, dass die Patienten zum Teil eine Vielzahl an unterschiedlichen Arzneimitteln einnehmen und Multimedikation vorliegt. Multimedikation erhöht nachweislich das Risiko für Stürze und Hüftfrakturen und führt somit auch zu mehr Krankenhausaufenthalten und einem Verlust der Selbstständigkeit der multimorbiden älteren Patienten [53,74]. Doch nicht nur die Anzahl der gefundenen Arzneistoffe ist wichtig, sondern auch die Art der Arzneistoffe, da Multimedikation ebenfalls ein Risikofaktor für die Einnahme von potentiell inadäquater Medikation und für die Einnahme von Anticholinergika beziehungsweise Arzneistoffe mit anticholinergen Nebenwirkungen darstellt [74,75]. Es konnte gezeigt werden, dass die Einnahme von PIM und/oder Anticholinergika mit einer verminderten kognitiven Funktion assoziiert ist. Deshalb muss eine rationale Verordnungs- und Verschreibungspraxis für die multimorbiden älteren Patienten stärker in den Fokus rücken. Gerade der Bereich des „Deprescribing“ ist ein guter Ansatz um die Anzahl der Arzneimittel pro Patient zu senken, um so vor allem potentiell inadäquate Medikation und Anticholinergika zu reduzieren oder gegen erprobtere beziehungsweise

nebenwirkungsärmere Arzneimittel auszutauschen. Dies sollte idealerweise in einem multidisziplinären Prozess durchgeführt werden. In der S3-Leitlinie der deutschen Gesellschaft für Allgemeinmedizin und Familienmedizin wird unter anderem darauf hingewiesen, dass durch die Zusammenarbeit von Hausärzten und Apothekern Studien aufzeigten, dass arzneimittelbezogene Probleme reduziert werden konnten, und die gewonnenen Daten auf eine verbesserte Verordnungsqualität, eine Reduktion von unangemessenen Verordnungen und eine Steigerung der Adhärenz hinwiesen [76]. Darüber konnte im Rahmen dieser Arbeit festgestellt werden, dass gerade mit der FORTA-Liste und dem ADS-Score – aber auch dem deutschen ACB-Score – gute Tools zur Verfügung stehen, um potentiell inadäquate Medikation und Arzneistoffe mit anticholinerger Wirkung zu identifizieren und den hausärztlichen und klinischen Arbeitsalltag zu erleichtern.

Zusammenfassend konnte festgestellt werden, dass multimorbide ältere Patienten einem sehr hohen Risiko für Multimedikation, der Einnahme von potentiell inadäquater Medikation und Anticholinergika ausgesetzt sind, wo durch die Arzneimitteltherapiesicherheit gefährdet ist. Dies verdeutlicht, dass wir verstärkt den Fokus auf eine adäquate Arzneimitteltherapie dieser vulnerablen und stetig wachsenden Patientengruppe legen müssen.

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ORIGINAL ARTICLE

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Non-random relations in drug use expressed as patterns comprising prescription and over-the-counter drugs in multimorbid elderly patients in primary care: Data of the exploratory analysis of the multicentre, observational cohort study MultiCare

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KEY MESSAGES

- This study revealed non-random and systematic relations in drug use – comprising prescription and over-the-counter drugs – expressed as drug patterns for multimorbid elderly patients in primary care in Germany.
- There are strong associations between drug patterns and multimorbidity clusters, which enrich the knowledge about the treatment of multimorbid elderly patients in primary care in Germany.

ABSTRACT

Background: The elderly population deals with multimorbidity (three chronic conditions) and increasinged drug use with age. A comprehensive characterisation of the medication – including prescription and over-the-counter (OTC) drugs – of elderly patients in primary care is still insufficient.

Objectives: This study aims to characterise the medication (prescription and OTC) of multimorbid elderly patients in primary care and living at home by identifying drug patterns to evaluate the relationship between drugs and drug groups and reveal associations with recently published multimorbidity clusters of the same cohort.

Methods: MultiCare was a multicentre, prospective, observational cohort study of 3189 multimorbid patients aged 65 to 85 years in primary care in Germany. Patients and general practitioners were interviewed between 2008 and 2009. Drug patterns were identified using exploratory factor analysis. The relations between the drug patterns with the three multimorbidity clusters were analysed with Spearman-Rank-Correlation.

Results: Patients (59.3% female) used in mean 7.7 drugs; in total 24,535 drugs (23.7% OTC) were detected. Five drug patterns for men (drugs for obstructive pulmonary diseases (D-OPD), drugs for coronary heart diseases and hypertension (D-CHD), drugs for osteoporosis (D-Osteo), drugs for heart failure and drugs for pain) and four drug patterns for women (D-Osteo, D-CHD, D-OPD and drugs for diuretics and gout) were detected. Significant associations between

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multimorbidity clusters and drug patterns were detectable (D-CHD and CMD: male: $\rho = 0.376$, CI 0.322–0.430; female: $\rho = 0.301$, CI 0.624–0.340).
Conclusion: The drug patterns demonstrate non-random relations in drug use in multimorbid elderly patients and systematic associations between drug patterns and multimorbidity clusters were found in primary care.

Introduction

The number and proportion of elderly people are growing worldwide due to demographic change. While, currently in Germany, 22% of the population is 65 years and older, the percentage of this age group is supposed to increase up to 33% in 2060 [1].

Elderly patients have an increased risk for multimorbidity and struggle with related problems like polypharmacy [2,3]. Polypharmacy is defined as the chronic co-prescription or co-application of different drugs at the same time. Common definitions state a number of five or more drugs [4–7]. Moreover, patients with multiple drug use are at risk for potentially inappropriate prescribing due to increased rates of adverse drug events and drug-drug interactions, possibly leading to prescription cascades and decreased health-related quality of life [6,8,9]. Existing clinical practice guidelines for treating chronic conditions are rarely applicable for multimorbid elderly patients because those patients are usually excluded from clinical trials [10]. In addition, multimorbidity and multiple drug use pose a massive challenge for general practitioners and other health care professionals because most clinical practice guidelines do not focus sufficiently on patients with numerous concurrent diseases [11]. Finding associations between drugs and diseases in treating multimorbid elderly patients is a crucial step to improve the health care needs of those patients.

MultiCare – a multicentre, prospective, observational, cohort study conducted in Germany – was set up to monitor disease interactions, progress and consequences of multimorbidity in elderly patients in primary care [12]. General practitioners (GP) were interviewed about their patients' health status and morbidities. GP's patients, among others, were interviewed about morbidities, prescription and OTC medication, health and functional status.

Previously, Schäfer et al. carried out an analysis about multimorbidity clusters of multimorbid elderly patients from the MultiCare cohort. Three multimorbidity clusters were detected, characterising different types of elderly multimorbid patients about their morbidities, socio-economic status and gender [13].

Until now, a comprehensive characterisation of the medication within the cohort of multimorbid elderly patients is still insufficient. In former studies, only prescription drugs were included for analysis and a healthier patient collective is presented by excluding patients from nursing homes and patients diagnosed with dementia, which are usually included in most other studies [4,14]. The objectives of the current study are: (I) to identify the relationships of different drugs or drug groups, including OTC drugs and to express these relationships as drug patterns and (II) to study how these drug patterns associate with previously published multimorbidity clusters in the same cohort [13].

Methods

Study design

MultiCare was conducted as a multicentre, prospective, observational cohort study of multimorbid patients in general practice. The study protocol is described in detail by Schäfer et al., but in brief, 158 general practices from eight study centres in Germany (Universities of Bonn, Dusseldorf, Frankfurt/Main, Hamburg, Jena, Leipzig, Mannheim and Munich) took part in the study [12]. Patients were included if they had at least three diagnosed chronic diseases and were between 65 and 85 years old. The following eight exclusion criteria were defined according to the study protocol: (I) nursing home patients, (II) blind, (III) deaf, (IV) patients with dementia, (V) life expectancy of fewer than three months, (VI) insufficient ability to read and speak German, (VII) patients who participate in other studies, (VIII) patients poorly known by the physician. Baseline data collection started in July 2008 and three follow-ups were performed. Each recruitment wave took 15 months. For our analysis, the baseline data collected from 2008 up to 2009 was used. GPs provided a list of all patients born between 01.07.1923 and 30.06.1943 from their medical records. Estimating a response rate of 40–50%, 50 patients from each surgery were contacted by study nurses and the trained scientists, and subsequently screened for inclusion and exclusion criteria. In total, 7172 patients out of 50,786 patients were contacted for

informed consent and 3317 patients could be included (total response rate: 46.2%). As 128 patients died before baseline interview took place, 3189 patients remained in the cohort. Trained scientists and study nurses conducted standardised interviews at patients' homes and at the general GP's surgeries using printed forms. The interviewers performed a brown bag review to collect all information about prescribed and OTC medication used by the patients within the last three months. The GP's were interviewed to gain information about patients' morbidity.

Ethics

The study was conducted in compliance with the Helsinki Declaration. The study protocol was approved by the Ethics Committee of the Medical Association of Hamburg in February 2008 and amended in November 2008 (Approval-No. 2881) and informed consent was obtained from all individual participants included in the study.

Drug categorisation

Utilised medicinal products were gathered using brown bag reviews, including OTC medicinal products (non-prescription medicinal products, including vitamin supplements and mineral supplements), gaining information about product name, German national drug code, dosage, pharmaceutical form and frequency. A brown bag review is a practice in which patients aid in medication reviews by putting all their medications in a bag and bringing them to their clinician for review [15]. Combined medicinal products were divided into single drugs, and were counted separately. Finally, single drugs (ATC 5th level) were classified using the official German version of the anatomical therapeutic chemical classification system (ATC) version 2016 [16]. To capture all OTC drugs, we coded homoeopathic and herbal traditional medicinal products under the group name herbal and homoeopathic agents.

Categorisation into prescription or OTC drugs was done following guidelines explained in the German regulation for prescribing medicinal products [17].

Multimorbidity clusters

The comprehensive description of the method on gaining the multimorbidity clusters and detailed results can be found in the publication of Schäfer et al. [13]. In summary, the patients' morbidity data were recorded from the GPs medical records. The diseases were classified based on the ICD10 code in 46 standardised diagnosis groups. By exploratory factor analysis three multimorbidity clusters were gained: (I) cardiovascular and metabolic disorders (CMD) cluster (hypertension, heart failure, dyslipidaemia, arrhythmia, diabetes mellitus, gout and other), (II) anxiety, depression, somatoform disorders and pain (ADS/P) cluster (chronic back pain, osteoporosis, asthma/chronic obstructive pulmonary disease and other) and (III) neuropsychiatric disorders (NPS) cluster (stroke, depression, heart failure, urinary incontinence and other). It was concluded that there were two different types of multimorbid elderly patients in the MultiCare cohort: Patients with cardiovascular and metabolic disorders that are often male, more aged and with low socio-economic status and patients with mainly ADS and pain-related morbidity and mostly female.

Statistical analysis

Descriptive analyses of the cohort were performed by calculating the frequencies of age, gender and collected drugs using Excel 2010 (Microsoft Office 2010 and 2016, Redmond, USA). For the following analysis SPSS 23/24 (IBM, Armonk, USA) was used. The Chi-Square-Test was exploited for calculating the gender dependency of OTC drug use. The Mann–Whitney-*U*-Test was used for determining the correlation between gender and number of taken drugs and the Spearman-Rank-Correlation was applied to analyse the effect of age on the number of drugs (significance level $p < 0.05$).

For exploratory factor analysis and scree plots STATA 12.1 (StataCorp, College Station, USA) was used. Drug patterns were detected using exploratory factor analysis because this technique permits the appearance of one variable in more than one factor [18]. For this analysis, the pharmacological subgroup (ATC 3rd level) was applied and the data were divided according to gender. All ATC codes with a prevalence of at least 5% were included to improve the epidemiological interest. A tetrachoric correlation matrix was used and the patterns were rotated oblimin to allow the data to correlate with each other. This technique was used by Schäfer et al. to gain the multimorbidity clusters, where the exact method is described in detail [13,19]. To determine the number of factors, we extracted the factors with the help of scree plots. An ATC code was associated with a drug pattern when the factorloading was at least 0.25. The extracted factors were valued by two pharmacists, two physicians and a psychologist. Patients were assigned to one pattern when they had at least received two of the

Table 1. Distribution of 24,535 drugs according to anatomical main group (ATC 1st level) and the top 20 ATC 5th level drugs (sorted according to their ATC 1st level) of 3189 patients of the MultiCare cohort and their proportion within the 1891 female patients in Germany (multiple use possible) (2008–2009).

ATC 1st level	ATC 5th level drugs	Frequency	Proportion per total number of drugs [%]	Proportion per patient [%]	Frequency for female (Proportion per female [%])
Cardiovascular system		9257	37.7		5162 (55.8%)
	Simvastatin	1114		34.9	526 (47.2%)
	Hydrochlorothiazide	1106		34.7	654 (59.1%)
	Ramipril	695		21.8	347 (49.9%)
	Metoprolol	661		20.7	375 (56.7%)
	Bisoprolol	629		19.7	368 (58.5%)
	Amlodipine	466		14.6	258 (55.4%)
	Torasemide	376		11.8	203 (54.0%)
	Enalapril	330		10.3	188 (57.0%)
	Lisinopril	216		6.8	109 (50.5%)
Alimentary tract and metabolism		5006	20.4		3286 (65.6%)
	Magnesium	765		24.0	541 (70.7%)
	Calcium	548		17.2	454 (82.8%)
	Omeprazole	448		14.0	278 (62.1%)
	Metformin	436		13.7	220 (50.5%)
	Cholecalciferol	392		12.3	337 (86.0%)
Nervous system		2507	10.2		1766 (70.4%)
Blood and blood forming organs		1904	7.8		955 (50.2%)
	Acetylsalicylic acid	1134		35.6	573 (50.5%)
	Phenprocoumon	441		13.8	215 (48.8%)
Musculo-skeletal system		1819	7.4		1186 (65.2%)
	Allopurinol	402		12.6	166 (41.3%)
	Diclofenac	390		12.2	268 (68.7%)
	Ibuprofen	335		10.5	244 (72.8%)
Respiratory system		1361	5.5		770 (56.6%)
Systemic hormonal preparations		999	4.1		773 (77.4%)
	Levothyroxine	616		19.3	504 (81.8%)
Genito-urinary system and sex hormones		568	2.3		241 (42.4 %)
Sensory organs		488	2.0		309 (63.3%)
Dermatologicals		190	0.8		123 (64.7%)
Antineoplastic and immunomodulating agents		154	0.6		122 (72.7%)
Various		106	0.4		67 (63.2%)
Antiinfectives		99	0.4		76 (76.8%)
Herbal and homeopathic agents		72	0.3		54 (75.0%)
Antiparasitic products		5	0.02		5 (100.0 %)

included ATC codes and could be assigned to multiple clusters.

To correlate the drug patterns and the previously published multimorbidity clusters the Spearman-Rank-Correlation was employed.

Results

Characterisation of the elderly, multimorbid patient collective

The MultiCare cohort includes 3189 patients aged between 65 and 85 years, 59.3% of which were women. We found 25,522 drugs from 875 different ATC 5th level codes. After excluding double ATC codes (2.0%) from single patients, 24,535 drugs (96.1%) were related to an ATC code. Patients used in mean 7.7 (± 3.9) drugs, the median was 7 (range 0 to 29) drugs (number of diagnosed chronic diseases: 7.0 ± 2.0 (13)).

Table 1 depicts the distribution of 24,535 drugs regarding the anatomical main groups (ATC 1st level), the top twenty chemical substances (ATC 5th level) of all patients and their proportion according to gender. The most common prescription drugs were simvastatin (34.9%), hydrochlorothiazide (34.7%) and ramipril (21.8%). The most common OTC drugs were acetylsalicylic acid as an antiplatelet agent (35.6%), magnesium (24.0%) and calcium (17.2%). Altogether, 23.7% of drugs were OTC drugs.

Subgroup analysis: gender and age

Concerning the detected ATC 5th level drugs, there was no statistically significant difference between the

Table 2. Loading of factors with eigenvalue ≥ 1 and cumulative percent for ATC 3rd level substances of 1298 male patients in Germany (2008–2009).

Male		D-OPD[a]	D-CDH[b]	D-Osteo[c]	D-HF[d]	D-Pain[e]
	Eigenvalue	3.60	3.32	2.59	2.52	1.92
	Cumulative percent [%]	7.61	14.99	22.17	29.22	35.36
ATC 3rd level		Factorloading				
A02B	Drugs for peptic ulcer and gastro-oesophageal reflux diseases					0.60
A10A	Insulins and analogues	−0.32		0.31		
A11C	Vitamin A und D, including combinations of the two			0.83		
A12A	Calcium			0.88		
A12C	Other mineral supplements			0.51		−0.34
B01A	Antithrombotic agents		0.85			
C01A	Cardiac glycosides				0.89	
C01D	Vasodilators used in cardiac diseases		0.46			
C03C	High-ceiling diuretics		0.29	0.32	0.47	
C03D	Potassium-sparing agents				0.34	
C07A	Beta blocking agents		0.62			
C08D	Selective calcium channel blockers with direct cardiac effect	0.55				
C10A	Lipid modifying agents		0.71			
M01A	Antiinflammatory and antirheumatic products, non-steroids					0.48
M05B	Drugs affecting bone structure and mineralisation			0.38	−0.26	
N02A	Opioids					0.77
N02B	Other analgesics and antipyretics					0.62
N06D	Anti-dementia drugs				−0.86	
R03A	Adrenergic inhalants	0.95				
R03B	Other drugs for obstructive airway diseases, inhalants	0.95				

[a]Drugs for obstructive pulmonary diseases; [b]Drug for coronary diseases and hypertension; [c]Drugs for osteoporosis; [d]Drugs for heart failure; [e]Drugs for pain.
The table expresses the eigenvalue for each factor, their cumulative percent (proportion of variance of the drug data, explainable by the patterns) and the factorloading of the ATC 3rd level substances, whereby factorloadings less than 0.25 were omitted. All ATC 3rd level substances loading with a factorloading of 0.25 or more on one factor were included in one of the described drug patterns. Negative factorloadings ≥ 0.25 express a negative association between the drugs and the drug pattern described.

prevalence in men and women. However, women were using significantly more drugs than men (7.9 ± 3.9 vs 7.4 ± 3.8 drugs, $p = 0.002$). The OTC drugs' proportion was highly significant within the female population (26.8% vs. 20.1%, $p < 0.001$).

There was no difference between the classes of detected drugs (ATC 5th level) and increasing age. Patients aged 65 up to 73.91 years old (median) used in mean 7.3 drugs concurrently while patients at the age of 73.91 up to 85 years used in mean 8.1 drugs at the same time. This allows the conclusion that with increasing age people used significantly more drugs ($p < 0.001$, $\rho = 0.103$).

Composition, frequencies and overlap of drug patterns

In both gender groups, 14 factors with an eigenvalue of 1 or higher were extracted. Applying scree plots, five factors within the male and four factors within the female population were extracted

Tables 2 and 3 show the composition of the different drug patterns with the associated factorloading. Drug patterns were named after diseases that were commonly treated with the included drugs, as follows: (I) drugs for chronic obstructive pulmonary diseases (D-OPD), (II) drugs for coronary diseases and hypertension (D-CDH), (III) drugs for osteoporosis (D-Osteo), (IV) drugs for heart failure (D-HF) and (V) drugs for pain (D-Pain) and the four drug patterns for women: (I) D-Osteo, (II) D-CDH, (III) D-OPD and (IV) diuretic drugs and drugs for gout (D-DG).

In total, 75.0% (973) of men and 45.2% (854) of women were relatable to at least one factor. Using this kind of model, a cumulative percent of 35.4% in the male cohort and 30.9% in the female cohort was detectable, expressing the proportion of variance of the drug data that can be explained by the pattern. The overlap of the factors separated by gender is shown in Figures 1 and 2, expressing that 33.8% (329) of men and 26.1% (223) of women could be assigned to at least two patterns. The most prevalent pattern for both genders was the D-CDH pattern (836 [64.4%] for men and 430 [22.7%] for women).

Comparison of drug patterns and multimorbidity clusters

The correlation between drug patterns and the recently published multimorbidity clusters is shown in Table 4 [13]. There is a moderate and significant correlation between male and female cardiovascular drug pattern and cardiovascular and metabolic disorder multimorbidity cluster (male: $\rho = 0.376$, $p < 0.001$, CI 0.322–0.430, female: $\rho = 0.301$, $p < 0.001$, CI

Table 3. Loading of factors with eigenvalue $\geq$ 1 and cumulative percent for ATC 3rd level substances of 1891 female patients in Germany (2008–2009).

Female					
		D-Osteo[a]	D-CDH[b]	D-OPD[c]	D-DG[d]
	Eigenvalue	4.11	3.75	2.35	1.95
	Cumulative percent [%]	9.14	16.92	24.68	30.85
ATC 3rd level		Factorloading			
A10A	Insulins and analogues		0.33		
A10B	Blood glucose lowering drugs, excl. Insulins	−0.26			
A11C	Vitamin A and D, including combinations of the two	0.96			
A12A	Calcium	0.91			
B01A	Antithrombotic agents		0.60		
C01A	Cardiac glycosides		0.83		
C01D	Vasodilators used in cardiac diseases		0.40		
C03A	Low-ceiling diuretics – thiazides				0.61
C03C	High-ceiling diuretics		0.65		
C03D	Potassium-sparing agents		0.27		0.65
M04A	Antigout preparations				0.75
M05B	Drugs affecting bone structure and mineralisation	0.84			
N04B	Dopaminergic agents			−0.43	
R03A	Adrenergic inhalants			0.94	
R03B	Other drugs for obstructive airway diseases, inhalants			0.96	
S01E	Antiglaucoma preparations and miotics				−0.31

[a]Drugs for osteoporosis; [b]Drug for coronary diseases and hypertension; [c]Drugs for obstructive pulmonary diseases; [d]Diuretic drugs and drugs for gout.
The table expresses the eigenvalue for each factor, their cumulative percent (proportion of variance of the drug data, explainable by the patterns) and the factorloading of the ATC 3rd level substances, whereby factor loadings of less than 0.25 were omitted. All ATC 3rd level substances loading with a factorloading of 0.25 or more on one factor were included in one of the described drug patterns. Negative factorloadings $\geq$ 0.25 express a negative association between the drugs and the drug pattern described.

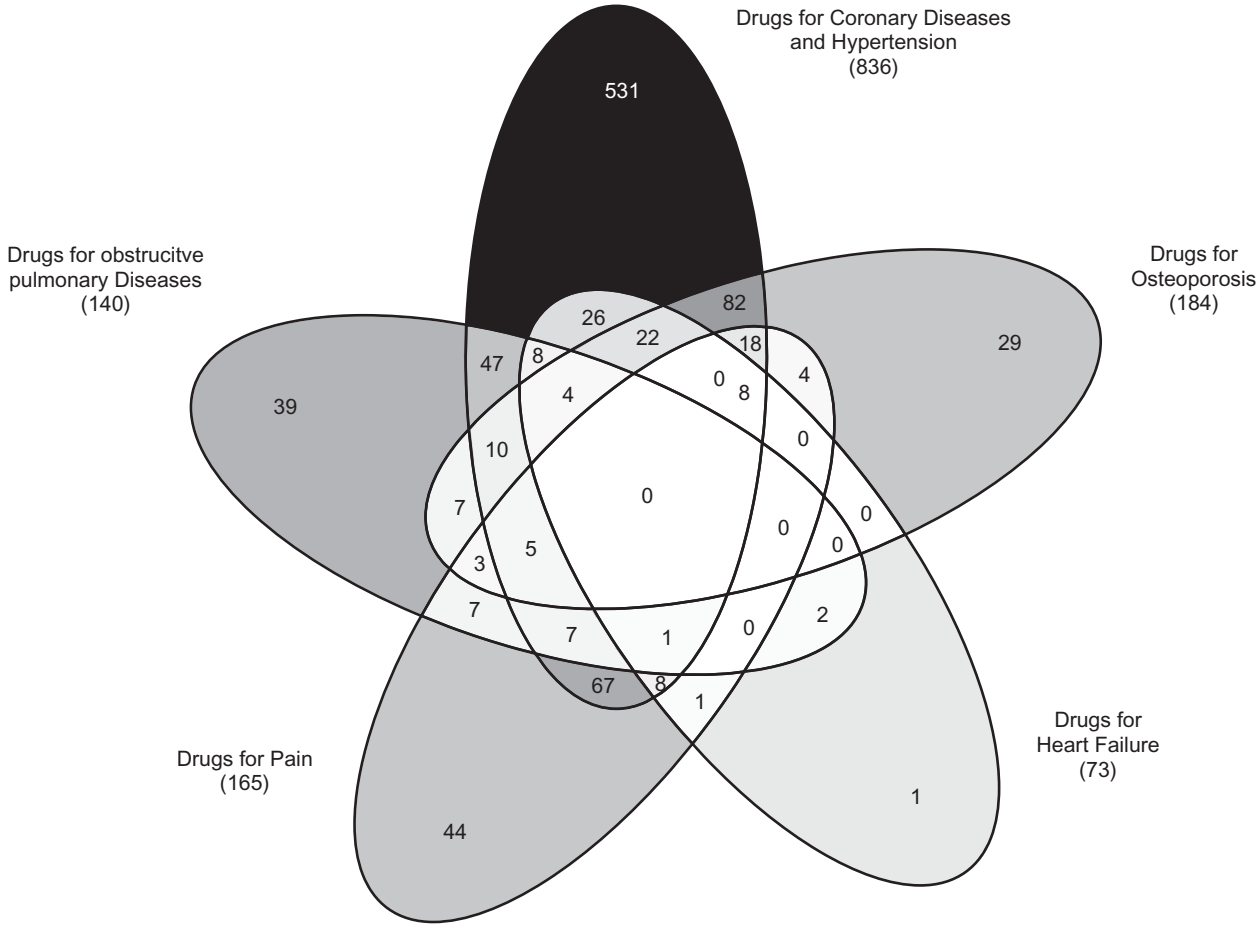

Figure 1. Overlapping of drug patterns (total number of patients) related to the total male population (1298) in Germany (2008–2009).

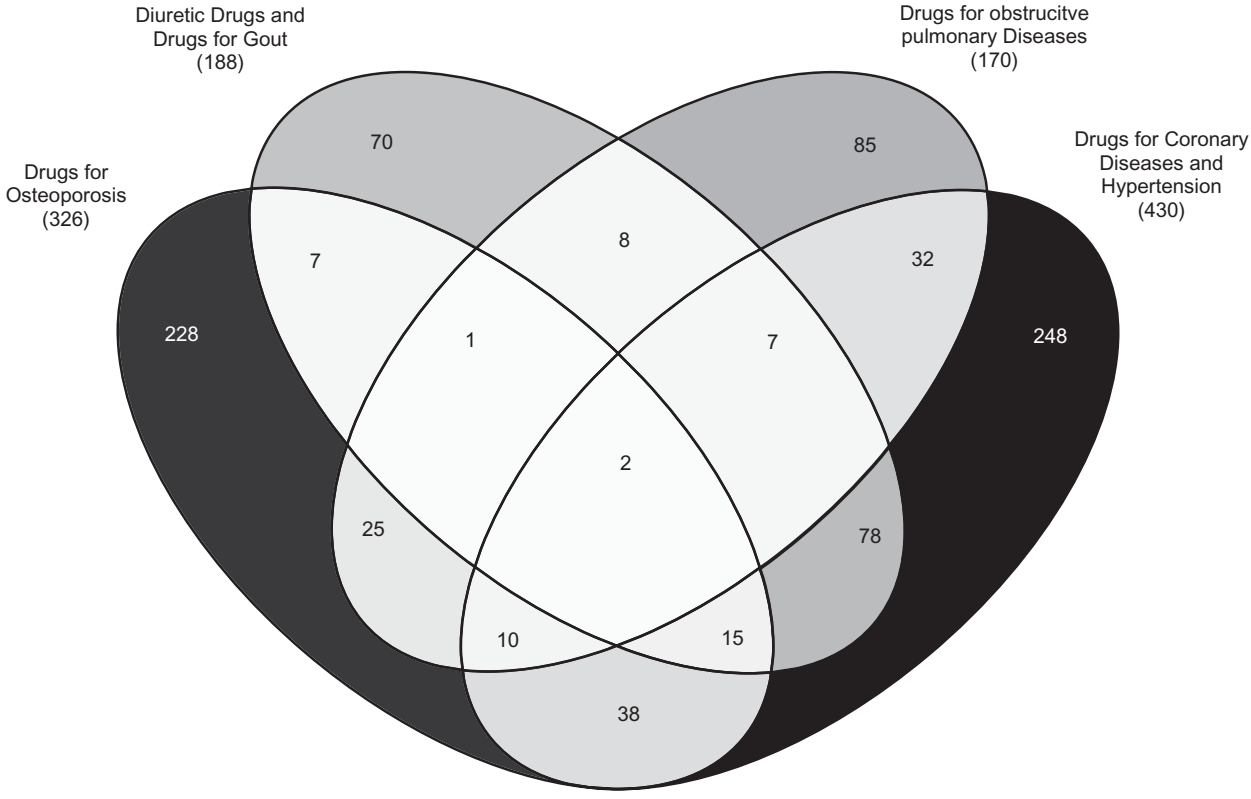

Figure 2. Overlapping of drug patterns (total number of patients) related to the total female population (1891) in Germany (2008–2009).

0.624–0.340). All other detected significant correlations appear with a small effect size ($\rho < 0.3$).

Discussion

Main findings

The 3189 multimorbid elderly patients aged 65 up to 85 years from the MultiCare cohort used 7.7 drugs concurrently. Cardiac drugs and electrolyte preparations like calcium and magnesium are prevalent in the patient cohort. Interestingly women used more OTC drugs than men and a small increased drug use with growing age was detectable.

Our study illustrates characteristic patterns in medication use in multimorbid elderly patients, with a high degree of overlap, pointing out multiple drug use and even polypharmacy. The identified drug patterns for men and women consist of different types of pharmacological subgroups; most of them comprise expectable and non-random drug combinations, exemplified by the D-Osteo and D-CDH pattern.

Strength and limitations

Even though the data provided by the MultiCare cohort study is from 2008 to 2009, we still have a well selected and representative patient cohort. By taking advantage of the carefully selected inclusion criteria, we can be confident that our results represent the German elderly, multimorbid population. Nonetheless, we might have some regional effects in prescribing because recruitment took place in large cities and rural areas were not covered. However, using the ATC 3rd level drugs is a common procedure to reduce the variability between different study centres [14].

High data quality was provided because interviewers and study nurses were trained and monitored regularly, and standardised interviews were conducted.

A limitation is that we did not know whether all drugs were taken regularly or on-demand. Nonetheless, the brown-bag procedure is a suitable method to collect data about OTC medication use. In this way, we are confident that we did not underestimate the drug use in contrast to most other studies.

The performed factor analysis is an appropriate method with regard to our objectives [20]. Four different methods were used and compared with each other to value the extracted factors and create a significant and reproducible result. We decided to follow the scree plots' results because they provide the most valid results and are a common method to extract

Table 4. Correlation coefficients ρ according to Spearman, p-values and 95% confidence interval of drug patterns and multimorbidity clusters for 3189 patients – separated for male and female – expressing the association between drug patterns and multimorbidity clusters from MultiCare study in Germany (2008–2009).

			95% confidence interval	
	ρ	p-Value	Min	Max
Male				
D-OPD[a] x CMD[g]	0.008	0.779	−0.049	0.063
D-OPD x ADS/P[h]	0.088	**0.002**	0.032	0.145
D-OPD x NPS[i]	−0.036	0.191	−0.047	−0.025
D-CDH[b] x CMD	0.376	**<0.001**	0.322	0.430
D-CDH x ADS/P	−0.089	**0.001**	−0.144	−0.037
D-CDH x NPS	0.031	0.266	−0.021	0.073
D-Osteo[c] x CMD	0.078	0.005	0.029	0.125
D-Osteo x ADS/P	0.019	0.486	−0.038	0.071
D-Osteo x NPS	0.022	0.434	−0.037	0.087
D-HF[d] x CMD	0.089	**0.001**	0.052	0.121
D-HF x ADS/P	−0.011	−0.704	−0.061	0.042
D-HF x NPS	0.007	0.804	−0.028	0.068
D-Pain[e] x CMD	−0.021	0.443	−0.081	0.037
D-Pain x ADS/P	0.103	**<0.001**	0.046	0.161
D-Pain x NPS	0.027	0.325	−0.033	0.101
Female				
D-Osteo x CMD	−0.112	**<0.001**	−0.155	−0.065
D-Osteo x ADS/P	0.102	**<0.001**	0.060	0.142
D-Osteo x NPS	0.002	0.918	−0.041	0.050
D-CDH x CMD	0.301	**<0.001**	0.264	0.340
D-CDH x ADS/P	−0.103	**<0.001**	−0.150	−0.056
D-CDH x NPS	0.232	**<0.001**	0.178	0.284
D-OPD x CMD	−0.003	0.902	−0.048	0.040
D-OPD x ADS/P	0.094	**<0.001**	0.053	0.135
D-OPD x NPS	−0.180	0.436	−0.057	0.026
D-DG[f] x CMD	0.157	**<0.001**	0.117	0.197
D-DG x ADS/P	0.0001	0.983	−0.045	0.044
D-DG x NPS	0.166	**<0.001**	0.056	0.172

[a]Drugs for obstructive pulmonary diseases; [b]Drug for coronary diseases and hypertension, [c]Drugs for osteoporosis; [d]Drugs for heart failure; [e]Drugs for pain; [f]Diuretic drugs and drugs for gout; [g]Cardiovascular and metabolic disorders; [h]Anxiety; depression; somatoform disorders and pain; [i]Neuropsychiatric disorders.
Significant p-values are marked in bold.

factors [14,18,20,21]. Some relations within the factors could occur because patients were included when they had at least three chronic diseases, which is a higher illness burden than included in most other studies. Nevertheless, in general, 44% of the patients in this age group apply to this definition of multimorbidity.

In contrast to other studies, an additional strength of our study is that patients from nursing homes and patients with dementia were excluded because of their inability to consent, forming a homogenous patient collective. Even though this might impact the generalisability of our data, we are already able to recognise effects like polypharmacy and patterns of drug use in a 'healthier' patient collective.

The results presented here are obtained from the baseline assessment of MultiCare cohort study. Longitudinal analysis is needed to confirm the detected drug patterns. Unfortunately, we are unable to explain all associations detected within the drug patterns. Analysis regarding the improvement of the understanding of multimorbidity and drug use in elderly patients is needed.

Interpretation of study results

Surprisingly, no ACE-inhibitors or angiotensin-II-antagonists were included in any pattern, although most guidelines recommended them for cardiac diseases as first-line therapy. However, as these drugs had a high prevalence (42.5% respectively 22.1%) in the whole cohort, it is possible that they are not specifically loading into one factor. Instead, cardiac glycosides are part of the D-HF pattern. These are recommended as an additional therapy for special indications after incomplete response for chronic heart failure patients [22,23]. Data collection started in July 2008, so it is possible that cardiac glycosides were still more common for the therapy of heart failure than nowadays, although guidelines barely changed since 2008 [24].

D-DG pattern – consisting of diuretic drugs and anti-gout preparations – demonstrates an association between the use of diuretics and gout, and that thiazides and thiazide-like diuretics significantly increase the risk of developing gout [25]. Furthermore, patients with renal insufficiency have a risk for increased uric acid levels.

The D-Pain pattern was only detectable for the male population. As women in our cohort used pain medication with a higher proportion than men, we assume that the frequent use of pain medication in the female population leads to the missing pain dimension.

The high degree of overlap between the drug patterns revealed that even in a presumed healthier patient collective, patients are already at risk for multiple drug use and even polypharmacy and are at risk for the associated negative consequences.

The distinct drug patterns can be associated with the multimorbidity clusters detected by Schäfer et al. [13]. Although we were only able to show this association with a small effect size – except for the higher association between the cardiovascular patterns in both gender groups – they are non-random and enrich the knowledge about the treatment of diseases. The different numbers of included patients might explain the small effect size and the multimorbidity clusters comprise a broader spectrum of diseases than drugs included in the drug patterns.

Comparison with other studies

Our data (mean: 7.7 drugs per patient) is in good accordance with published data about multimorbid elderly patients, Diez-Manglano et al. found a mean 8.2 (± 3.4) drugs per patient (mean age 81.0 ± 8.8 years) [26]. Studies showing lower numbers of drugs per patient usually did not include OTC drugs [4,14]. A study including OTC drugs found 23.4% OTC drugs per patient, confirming our findings of 23.7% [27]. Although we did not differentiate between dietary supplements and OTC drugs, we could show that women use more OTC drugs than men, which is in good accordance with literature and may result from higher health consciousness in women [28,29]. The slight increase in drug use with increasing age might be attributed to the fact that our cohort does not comprise patients living in nursing homes. As shown, patients residing in nursing homes use more drugs than patients living on their own [30].

Our results regarding the drug patterns are comparable with Calderón-Larrañaga et al., which is the only published study that also employed drug patterns in multimorbid elderly patients [14]. Using the same method as we did (differentiating in using an eigenvalue of 0.3), they detected seven drug patterns, that are quite similar to ours (cardiovascular-, depression-anxiety-, acute respiratory infection-, COPD-, rhinitis-asthma-, pain- and menopause pattern). Interestingly they detected a missing pain dimension in the female population, too.

Another study describing polypharmacy and morbidity patterns excluded patients older than 65 due to multicollinearity. Nevertheless, they also showed connections between multimorbidity and polypharmacy patterns, revealing similar findings for their age groups [31].

In contrast to other studies, the present MultiCare study focussed on the unique patient collective of multimorbid elderly patients by only including patients 65 years and older. In addition, our study is more outright by including OTC medication which forms a large part of patients' medication.

Implications for clinical practice

The high number of drug use and especially OTC drug use, detected among multimorbid elderly patients, points out the risk of drug-related problems and consequent negative influence on medication and patient safety in this vulnerable patient group. By discovering non-random associations of drug use we could confirm the results presented in other studies and successfully reproduce known knowledge about the drug therapy safety of multimorbid elderly patients [14,31]. The present study enriches the relations of multimorbidity and drug use in multimorbid elderly patients; this will help to improve the understanding of healthcare needs of multimorbid elderly patients. Further analysis regarding the adequacy of used medication in elderly multimorbid patients is needed.

Conclusion

This study points out relationships between prescription and OTC drugs in the multimorbid population aged 65 and older. The identified drug patterns – that partly indicate multiple drug use and polypharmacy due to the high degree of overlap – highlight non-random relations in drug use. By showing associations between drug patterns and multimorbidity clusters, we can gain new knowledge on multimorbid elderly patients' treatment in primary care and clinical routine. Further, the risk of multimorbidity and also polypharmacy is already visible in a presumed healthier patient collective.

With this study, we want to point out a greater awareness for this highly complex cohort and their treatment to improve the drug therapy of multimorbid elderly patients.

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3.2 Comparison of FORTA, PRISCUS and EU(7)-PIM list on identifying potentially inappropriate medication and its impact on cognitive function in multimorbid elderly German people in primary care: a multicentre observational study

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Comparison of FORTA, PRISCUS and EU(7)-PIM lists on identifying potentially inappropriate medication and its impact on cognitive function in multimorbid elderly German people in primary care: a multicentre observational study

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ABSTRACT

Objectives Our study aimed to assess the frequency of potentially inappropriate medication (PIM) use (according to three PIM lists) and to examine the association between PIM use and cognitive function among participants in the MultiCare cohort.

Design MultiCare is conducted as a longitudinal, multicentre, observational cohort study.

Setting The MultiCare study is located in eight different study centres in Germany.

Participants 3189 patients (59.3% female).

Primary and secondary outcome measures The study had a cross-sectional design using baseline data from the German MultiCare study. Prescribed and over-the-counter drugs were classified using FORTA (Fit fOR The Aged), PRISCUS (Latin for 'time-honoured') and EU(7)-PIM lists. A mixed-effect multivariate linear regression was performed to calculate the association between PIM use patients' cognitive function (measured with (LDST)).

Results Patients (3189) used 2152 FORTA PIM (mean 0.9±1.03 per patient), 936 PRISCUS PIM (0.3±0.58) and 4311 EU(7)-PIM (1.4±1.29). The most common FORTA PIM was phenprocoumon (13.8%); the most prevalent PRISCUS PIM was amitriptyline (2.8%); the most common EU(7)-PIM was omeprazole (14.0%). The lists rate PIM differently, with an overall overlap of 6.6%. Increasing use of PIM is significantly associated with reduced cognitive function that was detected with a correlation coefficient of −0.60 for FORTA PIM (p=0.002), −0.72 for PRISCUS PIM (p=0.025) and −0.44 for EU(7)-PIM (p=0.005).

Conclusion We identified PIM using FORTA, PRISCUS and EU(7)-PIM lists differently and found that PIM use is associated with cognitive impairment according to LDST, whereby the FORTA list best explained cognitive decline for the German population. These findings are consistent with a negative impact of PIM use on multimorbid elderly patient outcomes.

Trial registration number ISRCTN89818205.

Strength and limitations of this study

- From 3189 multimorbid elderly patients, medication was recorded using brown bag review, taking into account not only prescription medicines but also over-the-counter medicines.
- Drugs were categorised independently of dose according to PRISCUS and EU(7)-potentially inappropriate medication (PIM) lists because the daily dose and the frequency were not sufficiently documented.
- Since the FORTA list does not differentiate between drugs on demand or drugs taken regularly, all drugs were included in the analysis to allow comparability between the three PIM lists.
- The multivariate analysis and the multilevel models allow cluster effects.

INTRODUCTION

Medication management in multimorbid elderly patients is becoming more and more relevant because of ageing populations worldwide. Due to alterations in pharmacokinetics and pharmacodynamics, the risk for adverse drug events (ADEs) in older adults is increased.[1 2] In addition, elderly patients often suffer from multiple chronic conditions leading to a higher risk of hospitalisation.[3 4] Another risk factor in elderly patients

is multimedication that is associated with multimorbidity.[5 6] Multimedication, also known as 'polypharmacy', is defined as the coprescription of at least five drugs[7 8] and leads to a higher risk of drug–drug-interactions, drug–disease interactions and medication errors.[9–11] Moreover, elderly patients are especially vulnerable to potentially inappropriate medication (PIM), which is associated with decreased cognitive skills, frailty and falls.[12] The identification of PIM is an important step to improve medication safety and to optimise prescribing and also deprescribing in multimorbid elderly patients. Since the first PIM list was published by Beers, several tools from different countries have been published.[13] In our study, we decided to compare the following three screening tools, all of which are well suited for the German pharmaceutical market: FORTA (Fit fOR The Aged), PRISCUS (Latin for 'time-honoured') and EU(7)-PIM lists.[14–16] We wanted to compare a well-established, but 10-year-old, German national PIM list (PRISCUS) with a more currently updated and more comprehensive European PIM list (EU(7)-PIM list). As both lists are explicit tools and do not focus on individual patient's needs, we decided to include FORTA list as an implicit national PIM list in our analysis. The PIM lists provide a broad heterogeneity of the PIM included, which poses the question of whether they rate drugs similarly.

Although studies are examining PIM use in Germany using PRISCUS and EU(7)-PIM list, only a few offer large data from community-dwelling patients, and they do not investigate the association of PIM use on the cognitive function.[17–19] In addition, large studies often only use health insurance data and do not include over-the-counter (OTC) medication.[20] To the best of our knowledge, no study compares FORTA as an implicit PIM list with the two explicit PIM lists PRISCUS and EU(7)-PIM list for the same patient collective, especially concerning the association with a decrease in cognitive function. Since the risk of developing ADEs is even higher in patients with cognitive impairments.[21]

The prospective German cohort study MultiCare was conducted to investigate the consequences of multimorbidity in elderly patients in primary care. As part of MultiCare, general practitioners (GPs) and patients were interviewed about prescribed and OTC medications as well as health and functional status, thus enabling the present study.[22] The aims of the current study were (1) to examine and compare the frequency of PIM use identified via three different lists—FORTA list, PRISCUS list and EU(7)-PIM list; and (2) to examine and compare associations between PIM use according to each PIM list and to identify the PIM list that has the most impact on cognitive function.

METHODS

Study design

MultiCare—a multicentre, observational longitudinal cohort—recruited multimorbid patients from a total of 158 general practices in eight study centres in Germany (Universities of Bonn, Düsseldorf, Frankfurt/Main, Hamburg, Jena, Leipzig, Mannheim and Munich). Patients were randomly selected from the electronic files of GPs. Patient inclusion criteria were:at least three diagnosed chronic diseases and age between 65 and 85 years. Patients were excluded if they were nursing home residents; were blind and deaf; could not provide consent, particularly patients with dementia; had an expected life expectancy of fewer than 3 months; had insufficient ability to read and speak German; participated in other studies; and were poorly known by the physician. Out of 50 786 patients from the GP's electronic files, a random sample of 7172 were contacted for informed consent after screening for inclusion and exclusion criteria because of an estimated positive response rate of 40%–50%. Of those contacted, a total of 3317 (46.2%) responded and were willing to participate. A total of 128 patients were excluded retrospectively because they died before the baseline interview or due to other reasons. A total of 3189 patients were therefore included in our analyses. Morbidity was assessed in standardised GP interviews. Gender, age, education and income were collected in standardised patient interviews, which also comprised cognitive testing, using the letter digit substitution test (LDST). A brown bag review—gaining information about product name, German national drug code, pharmaceutical form, partly dosage, frequency and medication on demand or daily use—was performed at the patients' home, collecting information about OTC and prescription drugs used by the patients within the last 3 months. The analyses presented here are based on the baseline assessment, which took place between 21 July 2008 and 6 November 2009. Detailed information on the study design has been published previously by Schäfer *et al*[22 23] in the study protocol (online supplemental material 1).

FORTA list

The FORTA list, recently updated in 2018, includes 296 drugs used in the treatment of 30 diagnoses or indications. For each indication, the drugs were categorised by an expert Delphi panel into four categories: A (absolute), B (beneficial), C (careful) and D (don't). FORTA categories A and B are designed to detect potential undertreatment, whereas categories C and D signify drugs with questionable safety and effectiveness and can be used to identify PIM.[14]

PRISCUS list

The German PRISCUS list (last updated in 2011) includes 83 drugs from 18 drug classes. The list provides advice on treatment alternatives and necessary actions if the PIM use is unavoidable. The PRISCUS list was developed following a structured expert survey in a two-round Delphi process.[15]

EU(7)-PIM list

The EU(7)-PIM list is a European list for PIM based on different national PIM lists (German PRISCUS list, PIM lists from USA, France and Canada) published in 2015. The EU(7)-PIM list contains 282 drugs from 34 drug classes. The list comprises restrictions to dose and duration for some drugs and gives therapeutic alternatives and advice on dose adjustment. Two Delphi survey rounds with 30 experts were performed.[16]

PIM classification

Data on prescription and OTC drugs were gathered via brown bag review. The drugs were classified according to the anatomical therapeutic classification (ATC) system.[24]

Excel V.2016 and QlikView V.11.20 (QlikTech, Radnor, USA) were used to identify PIM according to the three different PIM lists.

Drugs were classified as potentially inappropriate according to PRISCUS and EU(7)-PIM list dose-independently. As the FORTA list does not differentiate between medication on demand or daily use, we decided to include all drugs into the analysis to enable comparability between the three lists. With FORTA, we screened patients' medication for FORTA A–D drugs. In contrast to the other two lists, FORTA classification depends on the diagnosis, so that several drugs are classified differently according to their indication. When there was no documented indication for the drug and the drug only occurred once in the FORTA list, we assumed the drug was taken for that indication. Where a drug has multiple entries, we only rated the drug as PIM (C and D), if an indication was documented.

Descriptive analysis of PIM use and subgroup analyses

Data analysis was conducted using Excel V.2016 and Stata V.15.1. Subgroups were selected according to gender, age (<80 years and ≥80 years) and the number of drugs used (median split: 0–7 drugs and 8–29 drugs). For each subgroup, we considered the number of PIMs used per person. To examine differences in PIM use by gender, age and the number of drugs used, a two-sample t-test with equal variances was performed.

Association of PIM use with cognitive function

A multivariate mixed-effect linear regression was performed to examine the associations between each of the three different PIM lists with cognitive function. The cognitive skills were determined via LDST.[25] The LDST is a speed-dependent cognitive task where patients have to replace letters by numbers in a specified time, as processing speed is an important cognitive ability for normal cognitive development and aging.[26] To account for regional variation between the eight different study centres (Bonn, Düsseldorf, Frankfurt/Main, Hamburg, Jena, Leipzig, Mannheim and Munich) and personal prescribing habits of the 158 general practices, we conducted a multilevel linear regression analysis adjusted for random effects on the study centre and GP practice with study centre level. We included gender, age, number of drugs used, number of diseases weighted by severity, highest education degree in the three groups according to the international CASMIN (**C**omparative **A**nalysis of **S**ocial **M**obility in **I**ndustrial **N**ations) classification and household net adjusted disposable income as independent variables into the model.[27] The missing values in LDST, number of diseases weighted by severity, education standard and the income data sets were imputed via hot-deck imputation. This procedure has been described in detail elsewhere.[22] Analyses were performed with the imputed data sets. To determine which PIM list has the most impact on the cognitive decline, the described model was extended to all three PIM lists. An alpha level of 5% ($p \leq 0.05$) was defined as statistically significant. All statistical tests were conducted using Stata V.15.1.

Patient and public involvement statement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for the design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

RESULTS

Characterisation of the study cohort

Table 1 describes the sociodemographic data of the patients. In the MultiCare cohort (3198 patients aged 65–85 years), 24 535 drugs, thereof 24.2% (5935) OTC, were identified and related to an ATC code (mean 7.7±3.9 drugs; median 7 drugs, range 0–29 drugs).

As shown in table 2, patients used PIM according to FORTA with a prevalence of 55.9%. In average, they used 0.9 (±1.0) FORTA PIM with a range of 0–7 PIMs per

Table 1 Sociodemographic data of 3189 patients at baseline

Age (years) (mean±SD)	74.4±5.2
Male (years) (mean±SD)	74.0±5.1
Female (years) (mean±SD)	74.7±5.3
Gender (%)	
Male	40.7
Female	59.3
Education (in CASMIN grade) (%)	
Low (grade 1)	62.3
Medium (grade 2)	26.8
High (grade 3)	10.9
Household-size adjusted net income per month (€) (mean±SD)	1412±704
Number of chronic conditions (mean±SD)	7.0±2.5
Number of taken drugs (mean±SD)	7.7±3.9

Table 2 Comparison of the descriptive results from FORTA, PRISCUS and EU(7)-PIM list

	FORTA PIM	PRISCUS PIM	EU(7)-PIM
Medication			
Total number (%) of drugs used	24 535	24 535	24 535
Prescribed	18 600 (75.8)	18 600 (75.8)	18 600 (75.8)
OTC	5935 (24.2)	5935 (24.2)	5935 (24.2)
Total number (%) of PIM	2852 (11.6)	963 (3.9)	4311 (17.6)
Prescribed	2474 (86.7)	939 (97.5)	3919 (90.9)
OTC	378 (13.3)	24 (2.5)	392 (9.1)
Median number of PIM (range)	1 (0–7)	0 (0–4)	1 (0–8)
Mean number of PIM (SD)	0.9 (±1.0)	0.3 (±0.6)	1.4 (±1.3)
Patients (%)			
Patients with at least one PIM	55.9	24.7	70.1
Patients with one PIM	1048 (32.9)	656 (20.6)	1020 (32.0)
Patients with two PIMs	496 (15.6)	123 (3.9)	678 (21.3)
Patients with three PIMs	168 (5.3)	15 (0.5)	320 (10.0)
Patients with four PIMs	47 (1.5)	4 (0.1)	140 (4.4)
Patients with five PIMs	19 (0.6)	–	50 (1.6)
Patients with six PIMs	3 (0.1)	–	19 (0.6)
Patients with seven PIMs	1 (0.03)	–	5 (0.2)
Patients with eight PIMs	–	–	2 (0.1)

FORTA, Fit fOR The Aged; OTC, over-the-counter; PIM, potentially inappropriate medication.

patient. PRISCUS PIMs were detected with a prevalence of 24.7%, and patients used PRISCUS PIM with a mean of 0.3 (±0.58) and with a range of 0–4. According to the EU(7)-PIM list, patients used 1.4 (±1.29) with a range of 0–8 PIMs. We detected EU(7)-PIM with a prevalence of 70.1%.

Regarding FORTA, we detected 2852 category C or D PIM in total and thereof 13.3% (378) OTC drugs. Divided by category, we identified a mean of 0.7 in category C FORTA PIM and 0.2 in category D FORTA PIM per patient. The most common category C PIM is phenprocoumone for the treatment of atrial fibrillation (441 patients, 13.8%), followed by ginkgo leaf preparations for the treatment of dementia (152, 4.8%), glimepiride for the treatment of diabetes mellitus (144, 4.5%) and verapamil for the treatments of hypertension and atrial fibrillation (116, 3.6%). The most common category D drugs are acetylic salicylic acid as antiplatelet agent for atrial fibrillation with 3.1% (100 patients), molsidomine (76, 2.4%), glibenclamide (69, 2.2%) and tocopherol (63, 2.0%).

We detected 963 PRISCUS PIM in total with a proportion of 2.5% (24) OTC drugs. The most common drugs were amitriptyline (88 patients, 2.8%), acetyldigoxin (60 patients, 1.9%), nifedipine (53 patients, 1.7%) and zopiclone (47 patients, 1.5%).

We identified 4311 drugs (17.6%) as EU(7)-PIM, and thereof 9.1% (392) were classified as OTC drugs. The most common drugs are omeprazole (448 patients, 14.0%), diclofenac (390 patients, 12.2%), ibuprofen (335 patients, 10.5%) and acetyl salicylic acid as analgesic (191, 6.0%).

Figure 1 illustrates the overlap between the three different PIM lists. Of the detected PIMs, 384 (6.7%) were identified within all three lists, while nearly all PRISCUS PIMs were also detected by EU(7)-PIM (97.9 %). Moreover, the summary of the top 20 PIMs used by the patients points out the small grade of overlap between the three PIM lists (table 3).

Subgroup analysis: age, gender and number of used drugs

Results of the subgroup analysis are described in table 4. Women were using significantly more PIM according to PRISCUS and EU(7)-PIM list (both p<0.001). Furthermore, patients who are 80 years old and older used more PIM according to FORTA and PRISCUS list (p=0.005 and p<0.001). In addition, we detected that patients using more than seven drugs at the same time used significantly more PIM according to all three PIM lists (all lists p<0.001). This effect was also detectable—in all three PIM lists—continuously with a growing number of used drugs (FORTA: 0.130, 95% CI 0.122 to 0.138, p<0.001; PRISCUS: 0.050, 95% CI 0.045 to 0.055, p<0.001; EU(7): 0.190, 95% CI 0.181 to 0.200, p<0.001).

Association with cognitive function

In table 5, the results of the LDST are shown. On average, patients achieved a mean score of 23 (±7.1) with a range

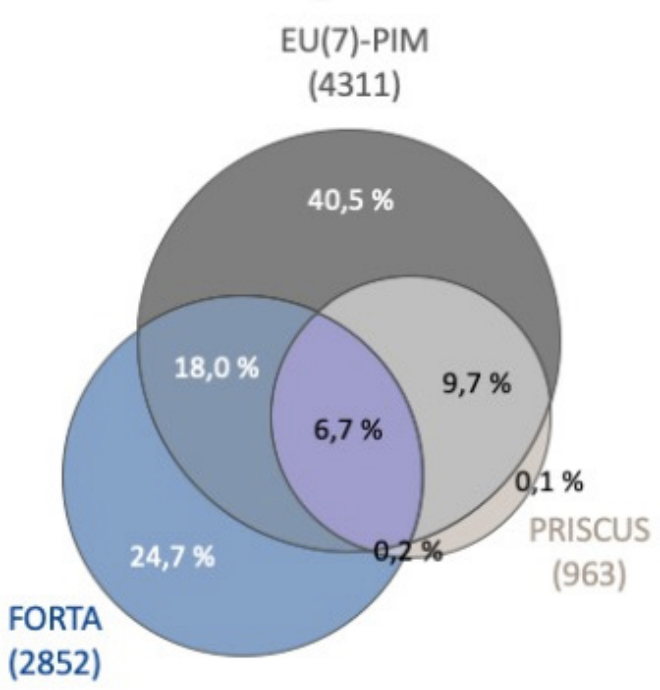

Figure 1 Venn diagram showing the overlap between FORTA, PRISCUS and EU(7)-PIM lists in terms of PIM (percentages sum up to 100%). FORTA, Fit fOR The Aged; PIM, potentially inappropriate medication.

of 0–50 in LDST. More than half of the patients (51.9%) scored between 20 and 29 in LDST.

We found that patients who used PIM scored significantly worse values in LDST than patients who used less or none PIM. This is true for all three PIM lists in a multivariate approach, with each PIM list analysed separately in the same regression model: FORTA-PIM (−0.397, 95% CI −0.644 to −0.150, p=0.002), PRISCUS (−0.464, 95% CI − 0.870 to −0.058, p=0.025) and EU(7)-PIM (−0.300, 95 CI% −0.508 to −0.092, p=0.005) (table 6).

By including all three PIMs in one regression model, the impact of FORTA (−0.306, 95% CI −0.567 to −0.044, p=0.022), PRISCUS (−0.118, 95% CI −0.652 to 0.276, p=0.428) and EU(7)-PIM list (−0.188, 95% CI −0.416 to 0.072, p=0.168) on the cognitive decline is shown (table 7). It appears that the association between PIM use and the patient's ability to complete the LDST is best depicted in the FORTA list.

DISCUSSION

Statement of principal findings

With the help of the three PIM lists, different numbers of PIM within the multimorbid elderly patients were detected. We identified that the use of PIM is associated with reduced cognitive function in multimorbid elderly patients. This was demonstrated for FORTA, PRISCUS and EU(7)-PIM lists. However, the FORTA list seems to be most suitable to reveal the association between PIM use and decreased cognitive function in multimorbid elderly patients.

Table 3 Top 20 drugs most commonly resulting in inappropriate prescribing according to FORTA, PRISCUS and EU(7)-PIM (drugs analysed in total 24 535)

PIM	FORTA	PRISCUS	Eu(7)-PIM
Omeprazole	–	–	448
Phenprocoumon	441	–	–
Diclofenac	–	–	390
Ibuprofen	–	–	335
Acetyl salicylic acid (analgesic)	–	–	191
Glimepiride	144	–	144
Pantoprazole	–	–	157
Ginkgo biloba leaves	152	–	–
Glimepiride	144	–	144
Verapamil	116	–	116
Moxonidine	114	–	114
Spironolactone	–	–	107
Tramadol	105	–	105
Theophylline	104	–	104
Acetyl salicylic acid (antiplatelet agent)	100	–	–
Amitriptyline	80	88	88
Digitoxin	32	–	93
Amitriptyline	80	88	88
Molsidomine	76	–	–
Tilidin	76	–	–

FORTA, Fit fOR The Aged.

PIM classification

In general, our data are in good accordance with recently published data. Other studies detected EU(7)-PIM with a prevalence of 57.2%–72.8%.[1 28 29] This seems to be comparable with our findings (70.1%). None of the three studies included OTC drugs, and in addition, Wauters *et al* included only patients 80 years and older.

The German ESTHER cohort detected PIM according to PRISCUS with a prevalence of 13.7% and according to the EU(7)-PIM list of 37.4%.[19] As they have a much younger patient collective—50 years–75 years—it is explainable that we found a higher prevalence in the MultiCare cohort (24.7% prevalence of PRISCUS PIM). Another reason for the higher observed PIM prevalences in detected EU(7)-PIM and PRISCUS PIM might be that only patients with at least three chronic diseases were included in our study. This is also apparent in a study including only patients with multimedication (five or more drugs) where the authors detected even higher prevalences of 45% PRISCUS PIM and 61% FORTA PIM (prevalence of FORTA PIM in our study: 55.9%).[30] The observed prevalence for PRISCUS PIM is quite lower than for FORTA and EU(7)-PIM. This is also following

Table 4 Difference between gender (male and female), the two different age groups (<80 years and ≥80 years) and between patients with zero to seven drugs at the same time and patients using more than seven drugs (8–29) at the same time measured with FORTA, PRISCUS and EU(7)-PIM list (significant p values marked in bold)

			PIM absolute					
		Patients (n)	(PIM (n)/drugs (n) (%))	Mean per patient	SD	Range	95% CI	P value
FORTA PIM	Male	1271	1126 (4.6)	0.89	1.00	0–5	0.83 to 0.94	
	Female	1876	1726 (7.0)	0.92	1.05	0–7	0.87 to 0.97	
								0.362
PRISCUS PIM	Male	1271	336 (1.4)	0.26	0.55	0–4	0.23 to 0.29	
	Female	1876	627 (2.6)	0.33	0.60	0–4	0.31 to 0.36	
								<0.001
EU (7)-PIM	Male	1271	1538 (6.3)	1.21	1.22	0–7	1.14 to 1.28	
	Female	1876	2773 (11.3)	1.48	1.33	0–8	1.42 to 1.54	
								<0.001
FORTA PIM	<80 years	2601	2293 (9.3)	0.88	1.02	0–7	0.84 to 0.92	
	≥80 years	546	559 (2.3)	1.02	1.08	0–6	0.93 to 1.11	
								0.005
PRISCUS PIM	<80 years	2601	744 (3.0)	0.29	0.57	0–4	0.27 to 0.31	
	≥80 years	546	219 (0.9)	0.40	0.62	0–3	0.34 to 0.45	
								<0.001
EU (7)-PIM	<80 years	2601	3519 (14.3)	1.35	1.29	0–8	1.30 to 1.40	
	≥80 years	546	792 (3.2)	1.44	1.31	0–8	1.33 to 1.55	
								0.145
FORTA PIM	0–7 drugs	1646	857 (3.5)	0.52	0.70	0–3	0.49 to 0.55	
	8–29 drugs	1501	1995 (8.1)	1.32	1.16	0–7	1.27 to 1.39	
								<0.001
PRISCUS PIM	0–7 drugs	1646	271 (1.1)	0.16	0.41	0–2	0.14 to 0.18	
	8–29 drugs	1501	692 (2.8)	0.46	0.69	0–4	0.43 to 0.50	
								<0.001
EU (7)-PIM	0–7 drugs	1646	1334 (5.4)	0.81	0.87	0–4	0.77 to 0.85	
	8–29 drugs	1501	2977 (12.1)	1.98	1.39	0–8	1.91 to 2.05	
								<0.001

FORTA, Fit fOR The Aged; PIM, potentially inappropriate medication.

Table 5 Descriptive results of LDST (imputed data: missing value 255 from 3189 patients) to measure the cognitive function of patients and the number of boxes patients were able to fill out correctly

	LDST
Mean (SD)	23.0 (±7.1)
Median (range)	23 (0–50)
Results LDST	**Patients (n)**
≤10 (relative)	78 (2.4%)
10 up to <20 (relative)	879 (27.6%)
20 up to <30 (relative)	1656 (51.9%)
30 up to <40 (relative)	533 (16.7%)
≥40 (relative)	43 (1.3%)

LDST, letter digit substitution test.

the aforementioned literature. These differences in the detected prevalences might occur due to the smaller number of drugs included in the PRISCUS list.

Moreover, the three PIM lists evaluate the drugs quite differently. For example, the PRISCUS list comprises more 'classic inappropriate' substances like antidepressants (18.2%), antihypertensives (5.7%) and hypnotics/sedatives (13.5%), which is also in good accordance with findings described in literature.[3 17 31] It is described that the prescriptions of sedatives, hypnotics, neuroleptics, antipsychotics and antihypertensives are risk factors for falls in elderly patients.[32] On the contrary, in addition to the classic potentially inappropriate substances, the FORTA list also identified as PIM those whose effectiveness had not been proven, for example, *Ginkgo biloba* and tocopherol. In addition, phenprocoumon is only listed in FORTA but not in PRISCUS or EU-(7) PIM, and it was the most common FORTA PIM. In V.2015 of FORTA,

Table 6 Multivariate linear regression model—impact of FORTA or PRISCUS or EU(7)-PIM use on cognitive function measured by LDST

LDST	Correlation coefficient	P value	95% CI
FORTA PIM per patient	−0.397	0.002	−0.644 to −0.150
Age	−0.340	<0.001	−0.383 to −0.296
Sex	2.538	<0.001	2.072 to 3.004
CASMIN3_2	2.348	<0.001	1.813 to 2.883
CASMIN3_3	3.791	<0.001	3.007 to 4.575
Income	2.407	<0.001	1.869 to 2.945
Number of diseases weighted by severity	−0.121	<0.001	−0.169 to −0.072
Number of taken drugs	−0.034	0.340	−0.105 to 0.036
PRISCUS PIM per patient	−0.464	0.025	−0.870 to −0.058
Age	−0.340	<0.001	−0.383 to −0.296
Sex	2.560	<0.001	2.093 to 3.026
CASMIN3_2	2.366	<0.001	1.831 to 2.901
CASMIN3_3	3.776	<0.001	2.992 to 4.561
Income	2.423	<0.001	1.885 to 2.961
Number of diseases weighted by severity	−0.127	<0.001	−0.176 to −0.079
Number of taken drugs	−0.060	0.079	−0.127 to 0.007
EU(7)-PIM per patient	−0.300	0.005	−0.508 to −0.092
Age	−0.344	<0.001	−0.387 to −0.300
Sex	2.597	<0.001	2.130 to 3.065
CASMIN3_2	2.351	<0.001	1.815 to 2.886
CASMIN3_3	3.772	<0.001	2.998 to 4.556
Income	2.409	<0.001	1.871 to 2.947
Number of diseases weighted by severity	−0.127	<0.001	−0.176 to −0.079
Number of taken drugs	−0.025	0.507	−0.101 to 0.050

Dependent variable: results from LDST; *independent variables*: FORTA PIM or PRISCUS PIM or EU(7)-PIM; *covariables* included in the regression model: sex, age, education standard (casmin3_2: comparison between medium and low educational standard; casmin3_3: comparison between high and low educational standard), number of diseases weighted by severity, income and number of taken drugs. Every PIM list is analysed separately in the same regression model.
FORTA, Fit fOR The Aged; LDST, letter digit substitution test; PIM, potentially inappropriate medication.

phenprocoumon was listed as a class B drug. However, with the availability of newer anticoagulants that do not require INR (international normalized ratio) monitoring, it has been recategorised as a FORTA C PIM in the updated version from 2018. Nevertheless, in most guidelines, phenprocoumon is still recommended.[33]

In addition to the substances detected with the PRISCUS list mentioned previously, proton pump inhibitors (PPIs) (15.7%) and NSAIDs (non-steroidal anti-inflammatory drug) (18.7%) were found to be the most common PIM in the EU(7)-PIM list. The high use of PPIs and NSAIDs is shown by some other studies as well.[1 28] But interestingly, in most studies, hypnotics and sedatives were found to be the most commonly prescribed EU(7)-PIM. We detected only 3.6% benzodiazepines, whereas other studies detected 4.2%–18.1% benzodiazepines, and therefore some studies presented only single substances.[1 28 34] Strikingly, there was only a small overlap between all three PIM lists. Although all three lists were developed for the German or European drug market, there is—besides some classic drugs—a broad heterogeneity in detected PIM. That raises the question of whether the use of only one PIM list is sufficient for the identification of PIM, leading to the assumption that already existing PIM lists need to be improved or even questioned to simplify and standardise this process. We need valid tools for identifying PIM because medication management in elderly multimorbid patients is highly complex. Detecting PIM and showing alternatives are still an important step to improve medication safety in multimorbid elderly patients.[12]

Risk factors for PIM use

To minimise the amount of prescribed PIM, we need to find out and, if possible, reduce risk factors for prescribing PIM. For example, we could demonstrate that multimedication is a risk factor for prescribing PIM in multimorbid elderly patients by pointing out that patients using seven drugs and more at the same time used significantly more

Table 7 Multivariate linear regression model—impact of FORTA, PRISCUS and EU(7)-PIM use on cognitive skills measured by LDST

LDST	Correlation coefficient	P value	95% CI
FORTA PIM per patient	−0.306	0.022	−0.567 to −0.044
PRISCUS PIM per patient	−0.118	0.428	−0.652 to 0.276
EU(7)-PIM per patient	−0.188	0.168	−0.416 to 0.072
Age	−0.172	<0.001	−0.384 to −0.296
Sex	−0.340	<0.001	2.114 to 3.050
CASMIN3_2	2.334	<0.001	1.799 to 2.869
CASMIN3_3	3.784	<0.001	3.000 to 4.567
Income	2.406	<0.001	1.868 to 2.943
Number of diseases weighted by severity	−0.121	<0.001	−0.170 to −0.073
Number of taken drugs	−0.004	0.921	−0.081 to 0.073

Dependent variable: results from LDST; *independent variables*: FORTA PIM, PRISCUS PIM, EU(7)-PIM; *covariables* included in the regression model: sex, age, education standard (casmin3_2: comparison between medium and low educational standard, casmin3_3: comparison between high and low educational standard), number of diseases weighted by severity, income and number of taken drugs.
All three PIM lists are included in one regression model.
FORTA, Fit fOR The Aged; LDST, letter digit substitution test; PIM, potentially inappropriate medication.

PIM. As multimedication is a well-described risk factor for prescribing PIM and is also associated with a higher risk of falls and hip fractures in multimorbid elderly patients, we must have the goal of rational prescribing.[31 35 36] Furthermore, the association between age and PIM use is inconsistent between the three PIM lists. Previous publications also showed different results.[21] We were also able to demonstrate that women are at higher risk of receiving PIM according to PRISCUS and EU(7)-PIM list but not according to FORTA. The observed gender differences in PIM use are in good accordance with the literature.[19 31] Moreover, Toepfer *et al* indicate that the female sex is at a greater risk of PIM use due to higher use of antidepressants, sleep-inducing drugs, analgesics and the use of oestrogens.[17]

Association of the use of PIM with the cognitive function

The relation between PIM use and the reduction of the cognitive function was based on poorer scores in a LDST, as determined by multivariate analysis. Other studies described that age, educational standard and gender influence LDST test results, so we decided—among others—to include those variables in our regression model.[25 37] In addition, the prescribing bias due to regional effects and the GPs were minimised by performing a multilevel regression. Muhlack *et al*[19] showed a strong cognitive impairment that is associated with PIM use according to EU(7), PRISCUS and Beers list. Beyond that, most studies that revealed the influence of PIM on cognitive function included patients with dementia.[21 38] Patients with dementia already have cognitive impairments due to their illness. In the MultiCare study, we excluded patients with all forms of dementia. Even though we cannot completely exclude the presence of already cognitively impaired patients in our study, we can show an effect of PIM use on the cognitive decline with less interference due to already cognitively impaired patients. Interestingly, in our model, the FORTA list best explained the decrease in cognitive function in multimorbid elderly patients. A possible explanation is that the FORTA list—in contrast to the PRISCUS and EU(7)-PIM lists—rates drugs based on indications as an implicit PIM list. Most other PIM lists are explicit tools and do not address the individual differences in patient needs. Furthermore, the FORTA list was developed for the German drug market and in contrast to the also German PRISCUS list, the FORTA list was recently updated in 2018. Another advantage is that the FORTA list is basically a positive and negative list because of the different categories. Also, the VALFORTA study points out the benefits of the FORTA list by showing that the use of the FORTA list reduced the occurrence of ADE and revealed overtreatment and undertreatment in elderly patients.[39]

Strength and limitations

There are some limitations with the present study. The PIM use according to the PRISCUS and EU(7)-PIM lists might have been overestimated in our study because we did not differentiate between medication on demand and regularly used medication. For example, omeprazole is inappropriate if it is used at maximum dosage for longer than 8 weeks without a clear indication. Furthermore, the daily dose was not documented consequently during the brown bag review. Due to this fact, it was not possible to categorise PIM—for the PRISCUS and EU(7)-PIM lists—according to their dosing.

The medication review was conducted at the patients' homes, via brown bag review. Additionally, patients were asked how the GPs told them to take their medication. It is therefore possible that a daily used NSAID, hypnotic, or PPIs has been labelled as medication on demand. As we did not want to underestimate the use of critical drugs

like PPIs, NSAIDs or hypnotics, we decided to count every drug that is documented as a PIM according to one of the three lists. In addition, almost all studies using large data analysed PIM irrespective of the dose, that is why we believe that this procedure is suitable for our patient collective.[17–20] However, this may lead to an overestimation of PIM use according to the PRISCUS and EU(7)-PIM lists. Therefore, we conducted a sensitivity analysis, excluding all medication on demand for PRISCUS and EU(7)-PIM. Both analyses still showed that there is an association between PIM according to the PRISCUS (−0.497, 95% CI −0.942 to −0.051, p=0.029) and EU(7)-PIM (−0.391, 95% CI −0.610 to −0.172, p<0.001) lists and a decreased cognitive function. Including all three PIM lists without medication on demand in one model, besides FORTA also the EU(7)-PIM list shows a significant association on patients' cognitive functions (FORTA: CC −0.269, 95% CI −0.534 to −0.003, p=0.047; EU(7)-PIM: - 0.275, 95% CI −0.536 to −0.014, p=0.039), while PRISCUS does not (−0.124, 95% CI −0.631 to 0.382, p=0.631).

FORTA PIM was analysed strictly indication-based, so it is possible that we even underestimated the sensitivity of the FORTA list. A strength of the data presented is that we included OTC drugs. Among the detected FORTA PIM and EU(7)-PIM, we had a high proportion of OTC drugs (13.3% and 9.1%). In addition, the number of OTC drugs might even have been underestimated because we counted NSAIDs and PPIs as prescription drugs because as they are prescribable for some indications due to the German medicines law. An additional strength consists of multivariate analyses, multilevel models allowing for cluster effects and advanced treatment of missing values.

Taken together, we were able to show that decreased cognitive function was apparent within all three PIM lists and that the FORTA list illustrates the cognitive decline most clearly. Besides that, the association between decreased cognitive function and the use of PIM underlines the importance of reducing the amount of PIM in elderly patients.

CONCLUSION

The supply of multimorbid elderly patients is a huge challenge we are facing, and therefore, we need to improve the medication safety of those patients. By identifying PIM with FORTA, PRISCUS and EU(7)-PIM lists and revealing that cognitive impairment is associated with PIM use, we can highlight the negative association of PIM use on elderly patients' outcomes and emphasise the importance of reducing the amount of PIM in elderly patients. To improve drug safety, it is important to have tools to identify PIM. However, the broad heterogeneity of detected PIM with the different tools also reflects that we still need to improve the already existing PIM lists.

Although we identified a high use of PIM among elderly multimorbid patients with different PIM lists, a longitudinal analysis is needed.

In summary, we identified PIM using FORTA, PRISCUS and EU(7)-PIM lists and revealed that PIM use is related to a decreased cognitive function. For the German population, the use of PIM detected by the FORTA list best explained the cognitive decline.

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3.3 Anticholinergic drug burden according to the anticholinergic risk scale and the German anticholinergic burden and their impact on cognitive function in multimorbid elderly German people: a multicentre observational study

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Anticholinergic drug burden according to the anticholinergic drug scale and the German anticholinergic burden and their impact on cognitive function in multimorbid elderly German people: a multicentre observational study

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ABSTRACT

Objectives The aims of our study were to examine the anticholinergic drug use and to assess the association between anticholinergic burden and cognitive function in the multimorbid elderly patients of the MultiCare cohort.

Setting MultiCare was conducted as a longitudinal cohort study in primary care, located in eight different study centres in Germany.

Participants 3189 patients (59.3% female).

Primary and secondary outcome measures Baseline data were used for the following analyses. Drugs were classified according to the well-established anticholinergic drug scale (ADS) and the recently published German anticholinergic burden (German ACB). Cognitive function was measured using a letter digit substitution test (LDST) and a mixed-effect multivariate linear regression was performed to calculate the influence of anticholinergic burden on the cognitive function.

Results Patients used 1764 anticholinergic drugs according to ADS and 2750 anticholinergics according to the German ACB score (prevalence 38.4% and 53.7%, respectively). The mean ADS score was 0.8 (±1.3), and the mean German ACB score was 1.2 (±1.6) per patient. The most common ADS anticholinergic was furosemide (5.8%) and the most common ACB anticholinergic was metformin (13.7%). The majority of the identified anticholinergics were drugs with low anticholinergic potential: 80.2% (ADS) and 73.4% (ACB), respectively. An increasing ADS and German ACB score was associated with reduced cognitive function according to the LDST (−0.26; p=0.008 and −0.24; p=0.003, respectively).

Conclusion Multimorbid elderly patients are in a high risk for using anticholinergic drugs according to ADS and German ACB score. We especially need to gain greater awareness for the contribution of drugs with low anticholinergic potential from the cardiovascular system. As anticholinergic drug use is associated with reduced cognitive function in multimorbid elderly patients, the importance of rational prescribing and also deprescribing needs to be further evaluated.

Trial registration number ISRCTN89818205.

Strengths and limitations of this study

- ► The well-selected exclusion criteria create a representative study population for the multimorbid elderly population.
- ► Gaining valid results by the advanced treating of missing values via hot deck imputation and the performance of a multivariate analysis.
- ► As the letter digit substitution test only addresses one aspect of cognition and cognitive impairment is a complex clinical symptom, further analyses are needed.

INTRODUCTION

The greater number of people in the population surviving until very late life leads to a challenge to the provision of healthcare, particularly given the proportion of older people that live with multiple comorbidities. These in turn often lead to polypharmacy, which is commonly defined as the coapplication or coprescription of five or more drugs at the same time.[1 2] Apart from this, it is also known that multimorbid elderly patients are at a higher risk for taking anticholinergic drugs or drugs that have anticholinergic side effects.[3] Besides classic anticholinergic substances—for example, drugs for urinary incontinence, chronic obstructive pulmonary disease or Morbus Parkinson—a lot of drugs

lead to anticholinergic adverse drug reactions (ADRs). These ADR and also the intended anticholinergic effects are evoked by the binding of drugs to one of the five muscarinic receptors in autonomous nervous system and especially blocking the parasympathetic nervous system.[4 5] Particularly elderly people are more vulnerable towards anticholinergic ADR because of an age-related decreased cholinergic transmission and a poorer metabolism and/or elimination of those substances.[6 7] Therefore, there is some evidence that the use of anticholinergic drugs or drugs with anticholinergic activity is associated with a higher risk of falls, hospitalisation and even mortality in elderly patients.[4 8–10] Anticholinergic drug use is also associated with cognitive impairments and dementia.[11–13] Moreover, the use of anticholinergics leads to less self-dependency and a decrease in functional status.[14] Likewise, patients might suffer from typical anticholinergic side effects as mental confusion, tremor, visual disturbances, delirium, dry mouth and urinary retention.[15]

The anticholinergic burden, the cumulative effect of using multiple drugs with anticholinergic activity simultaneously, can be calculated with the help of different lists.[16] In the most common lists, drugs are categorised in none, low, moderate or high anticholinergic activity (zero to three points). The gained scores are summed up, and when the score is greater or equal three points, one should consider to use alternative drugs or a dose reduction. Some lists additionally include the daily dose.[17] The number of included drugs varies between the scores and the scoring bases on different methods, for example, with regard to the drug's potency and efficiency or to its exposure.[18] With regard to the association of anticholinergic burdens on the cognitive function in elderly people, conflicting results have been published.[19] As the different published tools rate drugs quite differently and on different bases, we decided to use two different tools to evaluate anticholinergic burden of our patient collective.[18] The anticholinergic drug scale (ADS) developed by Carnahan *et al* is validated against serum anticholinergic activity (SAA), and high SAA levels are associated with cognitive impairments.[20 21] Furthermore, the ADS score is a well-established tool to identify drugs with anticholinergic activity. Kiesel *et al*[22] developed the German anticholinergic burden score (German ACB) especially for the German drug market in order to improve the routine prescribing in geriatric patients for the German population. To the best of our knowledge, there is no study that compares the ADS score with the German ACB score to investigate the anticholinergic burden of elderly multimorbid patients and pointing out the effect of anticholinergic drug use on the cognitive function. As far as we know, there is still limited data about the influence of anticholinergic drugs on the cognitive function from large European patient cohorts.

The German MultiCare cohort offers ideal conditions, as the study was conducted in order to examine the influence and effects of multimorbidity in multimorbid elderly patients in primary care. Patients and general practitioners (GPs) were interviewed about morbidities, prescribed and over-the-counter (OTC) medication, socioeconomic status, risk factors, health status and functional status, among others.[23]

The aims of our study were: (1) to identify anticholinergics and drugs with anticholinergic activity with the ADS and the German ACB score (2) and to show the effect of the anticholinergic burden measured with the German ACB score on the cognitive function and compare those findings with the well-established ADS score.

METHODS

Study design

The MultiCare study was carried out as a multicentre, observational cohort study in primary care. Baseline data collection started in July 2008, and three follow-ups were performed, and each recruitment wave took 15 months. For our analysis, the baseline assessment of 3189 patients, collected between 21 July 2008 and 6 November 2009, was used. The recruitment took place in eight study centres in Germany (Bonn, Duesseldorf, Frankfurt/Main, Hamburg, Jena, Leipzig, Mannheim and Munich). Multimorbid patients were randomly selected from the GPs' electronic files in 158 practices. Patients were included if they had at least three diagnosed chronic diseases and were between 65 and 85 years old. Exclusion criteria were: (1) nursing home patients, (2) blindness, (3) deafness, (4) missing capacity to consent, particularly patients with dementia, (5) all patients who had an expected life expectancy of less than 3 months, (6) insufficient ability to read and speak German, (7) patients who participate in other studies and (8) patients poorly known by the physician. A total of 7172 patients out of 50 786 patients from the GPs were contacted for informed consent after screening for inclusion and exclusion criteria. With a total response rate of 46.2%, 3317 patients were included, and after excluding 128 patients because they died before the baseline interview or due to other reasons, 3189 patients remained in the cohort. Standardised interviews and tests, at patients home, were conducted with the remaining 3189 patients to collect data about sex, age, education, income and cognitive skills by using the letter digit substitution test (LDST). Additionally, a brown bag review–capturing all prescription and OTC drugs the patients used on a regular basis or on demand–was performed to collect information about patients' medication. Information about morbidity was gained with the help of standardised GP interviews. Schäfer *et al* previously published detailed information on the exact study design[23 24] (online supplemental file 1).

Anticholinergic burden classification, descriptive results and subgroup analysis

Prescription and OTC drugs were gathered via brown bag review, and the drugs were classified analogous to the anatomical therapeutic classification (ATC) system.[25]

We used Excel 2016 (Microsoft Office 2016, Redmond, USA) to rate the anticholinergic drugs according to the German ACB and ADS scores.

The German ACB score was especially developed for the German drug market by Kiesel *et al*.[22] Drugs were classified as drugs with anticholinergic activity with the help of a systematic literature research in PubMed and a subsequently evaluation by experts. The German ACB score comprises 507 substances, whereby 356 drugs have no anticholinergic effect (ACB score=0), 104 drugs are scored as weak (ACB score=1), 18 drugs are scored as moderate (ACB score=2) and 29 drugs are scored as having strong (ACB score=3) anticholinergic effects.

The ADS comprises 413 substances and is based on expert opinions.[21] The ADS score categorises drugs into four different levels. Level 0 with no anticholinergic effect (296 substances), 71 level 1 drugs with a weak anticholinergic effect, 12 level 2 drugs with a moderate anticholinergic effect and 34 level 3 drugs with a strong anticholinergic effect.

The anticholinergic burden was calculated by summing up the individual anticholinergic scores of each patient, according to both anticholinergic scores individually.

For gaining the results for the subgroup analysis, a t-test with STATA V.15.1 (StataCorp, College Station, USA) was performed. We defined an alpha-level of 5% (p≤0.05) as statistically significant.

Fit for the Aged (FORTA) classification

For the classification according to FORTA PIM list, drugs were analysed indication based with QlikView 11.20 (QlikTech, Radnor, USA). The FORTA list comprises 296 drugs used in the treatment of 30 diagnoses or indications. FORTA rated drugs indication based as: A (absolute), B (beneficial), C (careful) and D (don't). Drugs were classified as a potentially inadequate medication (PIM) when they are a FORTA C or D drug.[26]

FORTA list is used to reveal whether an additional use of an anticholinergic burden classification is necessary or not.

Association of anticholinergic drug use with the cognitive function

We performed a multivariate mixed-effect linear regression to calculate the influence of anticholinergic burden detected by the German ACB and the ADS score on the cognitive skills of the patients. Whereby the LDST, as a speed-depending cognitive task, was used to calculate the cognitive skills of the multimorbid elderly patients.

In LDST, patients have to replace letters by numbers in a specific time to show their ability of processing speed, which is an important cognitive ability and expresses normal cognitive development.[27] Sex, age, number of diseases weighted by severity, highest education degree in three groups according to the international CASMIN (comparative analysis of social mobility in industrial nations) classification and household net adjusted disposable income as independent variables into the model were included.[28] We adjusted the multilevel linear regression for random effects on the study centre and GP practice in order to minimise the regional effect of prescribing because of the eight different study centres (Bonn, Dusseldorf, Frankfurt/Main, Hamburg, Jena, Leipzig, Mannheim and Munich) and the 158 general practices.

The missing values—in LDST (missing values: 243), number of diseases weighted by severity (152), education standard (3) and the income data sets (258)—were imputed via hot deck imputation. The hot deck imputation has been described elsewhere.[24] All analyses were performed with the imputed data sets, and an alpha level of 5% (p≤0.05) was defined as statistically significant. We conducted all statistical test with STATA V.15.1.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

RESULTS

Characterisation of the multimorbid elderly patient collective

A total of 3189 patients aged 65–85 years were included in the study. The mean age was 74.4 (±5.2) years and 59.3% of the patients were female. In total, 24 535 drugs including OTC were identified and related to an ATC code. In mean patients used 7.7 (±3.9) drugs (median 7 drugs, range 0–29 drugs). Table 1 summarises the main findings for the ADS and German ACB score. With ADS score, 1764 drugs were identified as anticholinergic for the MultiCare cohort, with a prevalence of anticholinergic drug use of 38.4% (1226). The mean ADS score is 0.8 (±1.3) and 10.5% (334) of all patients had an ADS score of 3 or higher. ForACB, we detected 2750 anticholinergics in total, and the prevalence of anticholinergic drug use is 53.7% (1714). The mean ACB score per patient is 1.2 (±1.6), and 18.1% (567) of all patients had an ACB score of 3 or higher.

As the most common ADS drug, we detected furosemide 5.8% (185) as anticholinergic with low potential. Amitriptyline was identified as the most common anticholinergic ADS drug with a high anticholinergic potential, with 2.8% (88). For the ACB score, we identified metformin with 13.7% (436) as an anticholinergic with low potential, as the most reported ACB anticholinergic in the MultiCare cohort. Tramadol with 3.3% (105) and amitriptyline with 2.8% (88) are the most common ACB anticholinergic drugs with a moderate and high anticholinergic potential, respectively. 80.2% of the anticholinergics according to ADS score and 73.4% of the detected anticholinergics according tothe German ACB score are low potential anticholinergic drugs. ADS score most frequently detected drugs from the cardiovascular system

Table 1 Anticholinergic drugs per patient according to anticholinergic drug scale (ADS) and the German anticholinergic burden (German ACB) score and anticholinergic score per patient according to ADS and the German ACB score

	ADS	ACB
Anticholinergic drugs per patient		
Number of anticholinergic drugs	1764 (7.2%)	2750 (11.2%)
Prevalence of anticholinergic drug use	38.4%	53.7%
Mean (SD)	0.6 (±0.9)	0.9 (±1.0)
Median (range)	0 (0–6)	1 (0–7)
0 AC per patient	1963 (61.6%)	1475 (46.3%)
1 AC per patient	846 (26.5%)	1033 (32.4%)
2 AC per patient	265 (8.3%)	435 (13.6%)
3 AC per patient	81 (2.5%)	172 (5.4%)
4 AC per patient	26 (0.8%)	45 (1.4%)
5 AC per patient	7 (0.2%)	24 (0.8%)
6 AC per patient	1 (0.03%)	4 (0.1%)
7 AC per patient	–	1 (0.03%)
Anticholinergic score per patient		
Mean (SD)	0.8 (±1.3)	1.2 (±1.6)
Median (range)	0 (0–11)	1 (0–11)
Score per patient: 0	1963 (61.6%)	1475 (46.3%)
Score per patient: 1	682 (21.4%)	802 (25.1)
Score per patient: 2	210 (6.6%)	345 (10.8%)
Score per patient: 3	179 (5.6%)	272 (8.5%)
Score per patient: 4	86 (2.7%)	140 (4.4%)
Score per patient: 5	36 (1.1%)	67 (2.1%)
Score per patient: 6	23 (0.7%)	45 (1.4%)
Score per patient: 7	5 (0.2%)	21 (0.7%)
Score per patient: 8	2 (0.1%)	14 (0.4%)
Score per patient: 9	2 (0.1%)	5 (0.2%)
Score per patient: 10	–	1 (0.03%)
Score per patient: 11	1 (0.03%)	2 (0.1%)

AC, anticholinergic.

Table 2 Top 10 anticholinergics according to anticholinergic drugs scale (ADS) and the German anticholinergic burden (ACB) score and their occurrence in Fit for the Aged (FORTA) list (in brackets: ADS/ACB levels and FORTA categories)

	ADS (level)	ACB (level)	FORTA PIM (categories)
Metformin	–	436 (1)	436 (B)
Furosemide	185 (1)	185 (1)	185 (B)
Tiotropium (inhalative)	–	125 (1)	–
Triamterene	107 (1)	107 (1)	98 (B)
Tramadol	105 (1)	105 (2)	105 (C)
Theophylline	104 (1)	104 (2)	104 (C)
Prednisolone	103 (1)	–	103 (B)
Digitoxin	93 (1)	93 (1)	32 (C)
Amitriptyline	88 (3)	88 (3)	49 (C) und 31 (D)
Ipratropium (inhalative)	–	84 (1)	–

ADS and German ACB level 1–3 rate drugs in low, middle and high anticholinergic risk. FORTA categories rate drugs as A (absolute), B (beneficial), C (careful), D (don't), whereby C and D drugs are defined as potentially inappropriate medication.

(ATC C) with 36.6% (646 drugs, 11 different substances), followed by drugs from the nervous system (ATC N) with 31.9% (563 drugs, 35 different substances). In contrast, drugs from the nervous system make up the largest group of identified ACB anticholinergics, with 50 different substances and 29.5% (812 drugs) in total, followed by the cardiovascular system, with 13 different substances and 25.7% (709 drugs) in total. Considering the distribution of all used drugs within the MultiCare cohort, the proportions of anticholinergic drugs according to ADS and German ACB with regard to drugs from the cardiovascular system are 7.0% and 7.7% and with regard to drugs from the central nervous system are 22.5% and 32.4%, respectively.

In table 2, the top 10 ADS and German ACB anticholinergics and their occurrence in the FORTA PIM list are captured. Two of the top 10 drugs (tiotropium and ipratropium as inhalatives) are not listed in the FORTA list, while only four drugs are classified into the categories C or D.

Subgroup analysis: age, sex and polypharmacy

Tables 3 and 4 summarise the most important results of the subgroup analysis for both scores. Female patients had a significant higher ADS and German ACB score than male patients (ADS: female: 0.82±1.34 male: 0.65±1.15; p<0.001; ACB: female: 1.30±1.73and male: 1.04±1.42; p<0.001). Patients 80 years old and older had a significant higher ADS score than the patients that are 65 up to 79 years old (p=0.001). In contrast with that, there was no significant effect on the ACB score observed between the two age groups. However, patients using eight drugs or more at the same time had a significant higher ADS and ACB score than patients using less drugs (p<0.001).

Association of anticholinergic drug use with the cognitive function

On average, patients achieved a mean LDST score of 23 (±7.1) with a range of 0–50 in the LDST, while 51.9% of the patients gained a score between 20 and 29. Figure 1 shows the kernel density estimator of the baseline results of patients LDST, showing the proportion of patients in each category.

Table 3 The influence of age, sex and the number of taken drugs on the anticholinergic drug use according to anticholinergic drug scale (ADS) score in multimorbid elderly patients (significant p values are marked in bold)

ADS score	Number of patients	Mean	SD	Range	95% CI	P value
<80 years	2635	0.71	1.24	0–11	0.67 to 0.76	
≥80 years	554	0.91	1.38	0–9	0.79 to 1.02	
						p=0.001
Male	1298	0.65	1.15	0–8	0.58 to 0.71	
Female	1891	0.82	1.34	0–11	0.76 to 0.86	
						p<0.001
0–7 drugs	1688	0.36	0.82	0–9	0.33 to 0.4	
8–29 drugs	1501	1.18	1.52	0–11	1.1 to 1.25	
						p<0.001

We evolved two models to express the influence of anticholinergics on the LDST results. Tables 5 and 6 show the outcomes of the multivariate mixed-effect linear regression for the ADS score and the German ACB score. In the first model, not including FORTA PIM, we detected that with increasing ADS score, the ability to complete the LDST decreases significantly with a regression coefficient of – 0.37 (p≤0.0001). Also, the German ACB score could exhibit the effect of worse LDST results with increasing ACB score with a regression coefficient of – 0.33 (p≤0.0001). According to a sensitivity analysis, we added FORTA PIM as a cofounder to the regression model (ADS score: p=0.257, regression coefficient: –0.04; ACB score: p=0.518; regression coefficient: –0.02). By adding FORTA PIM into the second model, the regression coefficient dropped but was still significant: for ADS score, we measured a regression coefficient of –0.26 (p=0.008) and for the German ACB, a score of –0.24 (p=0.003).

Table 4 The influence of age, sex and the number of taken drugs on the anticholinergic drug use according to German anticholinergic burden (ACB) score in multimorbid elderly patients (significant p values are marked in bold)

ACB score	Number of patients	Mean	SD	Range	95% CI	P value
<80 years	2635	1.18	1.61	0–11	1.12 to 1.24	
≥80 years	554	1.27	1.62	0–9	1.14 to 1.41	
						p=0.1992
male	1298	1.04	1.42	0–9	0.96 to 1.11	
female	1891	1.30	1.73	0–11	1.22 to 1.38	
						p<0.001
0–7 drugs	1688	0.60	1.02	0–9	0.56 to 0.65	
8–29 drugs	1501	1.86	1.87	0–11	1.76 to 1.95	
						p<0.001

DISCUSSION

Statement of principal findings

Our study demonstrates that a huge proportion of multimorbid elderly patients are exposed to anticholinergic drugs or drugs with anticholinergic activity and are consequently affected by the risk of anticholinergic adverse reactions that are associated with decreased cognitive function determined by LDST.

Anticholinergic burden classification and risk factors for anticholinergic drug use

In terms of the ADS score, our findings are in good accordance with the literature.[29–31] As there is no publication analysing medication with the German ACB score yet, we compared our findings with the gained results of the ADS score and other well-established anticholinergic scores. The results for the German ACB score (mean anticholinergic burden: 1.2±1.6; prevalence: 53.7%) are comparable with our findings with the ADS score (0.8±1.3; 38.4%) and also other anticholinergic scores described in literature (0.3±0.7 to 1.7±1.5; 17.1%–63.0%).[10 29]

Even though we determined that drugs from the central nervous system are the most common drugs identified with the German ACB score and the second most common for ADS, our top 10 anticholinergic drugs showed a more diverse spectrum of drugs. Particularly, drugs with low to moderate anticholinergic effects occurred in our top 10 list for both scores. As 80.2% of the anticholinergic drugs according to ADS and 73.4% of the anticholinergic drugs according to German ACB are anticholinergics with a score of 1, it is important to also focus on the drugs with only mild anticholinergic potential during prescribing and reviewing patients' medications. Furthermore, drugs treating cardiovascular conditions highly contributed to the level 1 anticholinergic drugs in both scores. However, in multimorbid elderly patient, it is common to coprescribe drugs like furosemide, triamterene, digitoxin and captopril to treat multiple conditions.[32] Also other studies point out the high prevalence of low potential anticholinergic drug use and especially from the cardiovascular system in elderly patients.[32 33] It is stated that especially the cumulative anticholinergic effect contributes to higher anticholinergic scores and even leads to hospitalisation and higher risk for mortality.[34–36] A lot of the mentioned and detected level 1 drugs are peripherally acting anticholinergic drugs. However, as the permeability of the blood–brain barrier is increased and at the same time the P-glycoprotein function is decreased with growing age, elderly people are more vulnerable towards anticholinergic ADRs.[5]

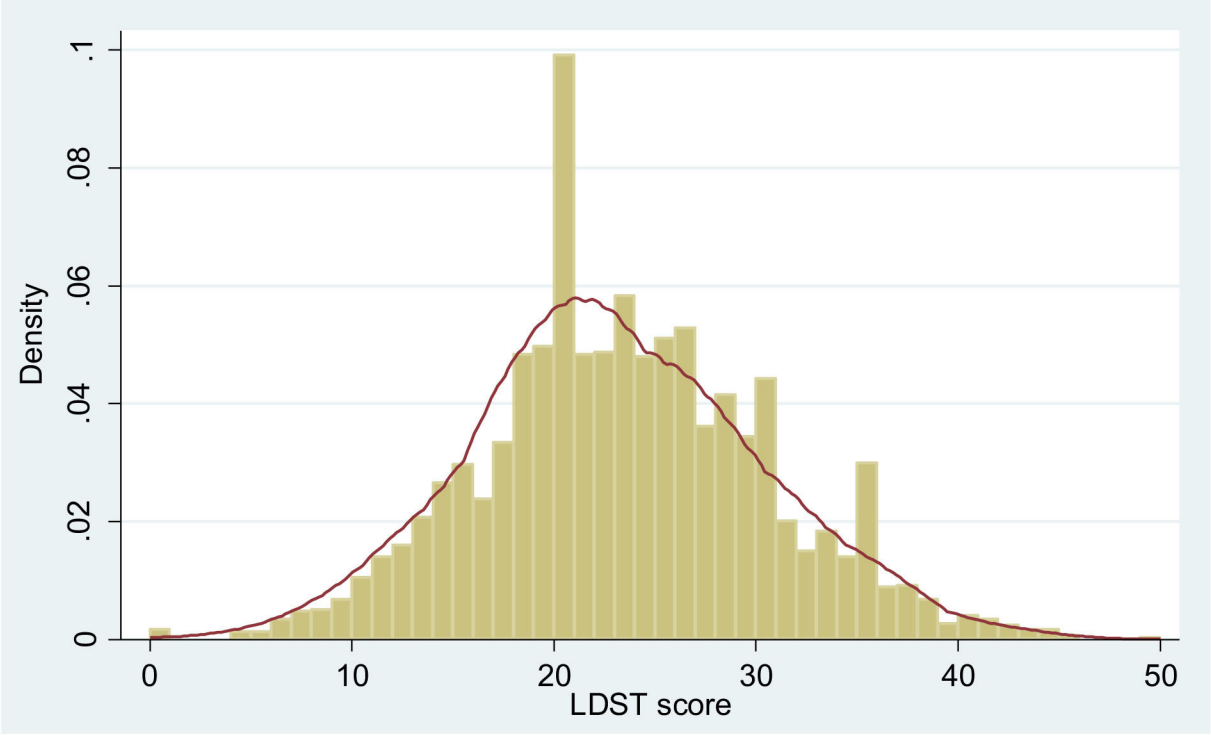

Figure 1 Kernal density estimator for the baseline assessment of the letter digit substitution test with the purpose of measuring the cognitive function of patients and the number of boxes patients were able to fill out correctly in a defined time. LDST, letter digit substitution test.

Particularly multimorbid elderly patients are vulnerable for polypharmacy.[37 38] So it is not surprising that we identified polypharmacy as risk factor for a high German ACB and ADS score. Besides this, we detected that female patients seem to be more vulnerable towards the exposure with anticholinergic drugs. This gender shift was also observed in several studies, although most studies used different tools to identify the anticholinergic burden.[15 30 39] The increased vulnerability of women towards anticholinergic drug exposure might be explainable by the fact that women have a higher health awareness than men.[40] In addition, rates of depression are higher in the female population, and we identified drugs from the central nervous system as one of our largest drug groups contributing to the anticholinergic burden.[41]

Association of anticholinergic drug use with the cognitive function

Multivariate analysis revealed that a higher anticholinergic burden according to ADS and also the German ACB score is associated with a decreased cognitive function according to an increasing poorly performance in the LDST. Interestingly, the newly developed German ACB score showed similar results in our adjusted model in comparison with the already well-established ADS score. A lot of studies prove that a high anticholinergic burden is associated with a decreased cognitive function as well.[35 42] However, there are also opposite findings. For example, Kersten *et al*[31] could determine that there was no association between cognitive impairments and anticholinergic drug use according to ADS score. The differences in the outcomes might be explained by several factors. First, it is sometimes difficult to show a homogenous association between anticholinergic drug use and cognitive function, because there is a broad heterogeneity in cholinergic brain reserve in each individuum that leads to differences in the sensitivity to central anticholinergic effects, and second, the used tools for detecting anticholinergic drugs and drugs with anticholinergic activity and measuring the cognitive function of the patients differs between the studies and not always fits the country-specific prescribing habits.[43] However, Gray *et al*[44] detected in a prospective cohort study over a time period of 7.3 years that 23% of the patients 65 years old and older develop a dementia and thereof 80% used anticholinergic drugs. As already mentioned, patients were excluded from MultiCare study when they were diagnosed with dementia and/or were living in nursing homes. Even though there was no standardised tool for diagnosing dementia due to the different GPs in the different study centres, we can assume that our patient collective had less cognitive impairments than the collectives in other studies. So it is quite interesting that our patient collective already shows an association between decreased cognitive function based on poorer results in LDST and a high anticholinergic score. That demonstrates the importance of rational prescribing and also deprescribing, even in presumed healthier elderly patients. Drugs with anticholinergic activity are widely prescribed, but we need to evaluate the pros and cons of their usage. On the

Table 5 The two linear regression models for the association between cognitive function (LDST) and anticholinergic score according to anticholinergic drugs scale (ADS) score (significant p values are marked in bold)

LDST	Regression coefficient	P value	95% CI
ADS score per patient	−0.37	**<0.001**	−0.55 to −0.2
Sex	−0.34	**<0.001**	−0.38 to −0.3
Age	2.57	**<0.001**	2.11 to 3.04
Casmin3_2	2.33	**<0.001**	1.8 to 2.87
Casmin3_3	3.68	**<0.001**	2.91 to 4.45
Income	2.45	**<0.001**	1.92 to 2.98
Number of diseases weighted by severity	−0.13	**<0.001**	−0.18 to −0.09
ADS score per patient	−0.26	**0.008**	−0.46 to −0.07
Sex	−0.34	**<0.001**	−0.38 to −0.3
Age	2.58	**<0.001**	2.12 to 3.04
Casmin3_2	2.32	**<0.001**	1.79 to 2.85
Casmin3_3	3.71	**<0.001**	2.94 to 4.48
Income	2.44	**<0.001**	1.91 to 2.97
Number of diseases weighted by severity	−0.12	**<0.001**	−0.16 to −0.07
FORTA PIM	−0.35	**0.005**	−0.59 to −0.11

Dependent variable: results from LDST; independent variable: ADS score; covariables included in the regression model: sex, age, education standard (casmin3_2: comparison between medium and low educational standard; casmin3_3: comparison between high and low educational standard), income, number of diseases weight by severity, used FORTA drugs.
ACB, anticholinergic burden; FORTA, Fit for the Aged; LDST, letter digit substitution test.

Table 6 The two linear regression models for the association between cognitive function (LDST) and anticholinergic score according to the German anticholinergic burden (ACB) score (significant p values are marked in bold)

LDST	Regression coefficient	P value	95% CI
ACB score per patient	−0.33	**<0.001**	−0.47 to −0.19
Sex	−0.34	**<0.001**	−0.39 to −0.3
Age	2.60	**<0.001**	2.14 to 3.06
Casmin3_2	2.33	**<0.001**	1.8 to 2.86
Casmin3_3	3.68	**<0.001**	2.9 to 4.45
Income	2.42	**<0.001**	1.89 to 2.95
Number of diseases weighted by severity	−0.13	**<0.001**	−0,17 to −0,08
ACB score per patient	−0.24	**0.003**	−0.40 to −0.08
Sex	−0.34	**<0.001**	−0.39 to −0.30
Age	2.60	**<0.001**	2.13 to 3.06
Casmin3_2	2.32	**<0.001**	1.79 to 2.85
Casmin3_3	3.70	**<0.001**	2.93 to 4.47
Income	2.42	**<0.001**	1.89 to 2.95
Number of diseases weighted by severity	−0.12	**<0.001**	−0.17 to −0.07
FORTA PIM per patient	−0.29	**0.030**	−0.54 to −0.03

Dependent variable: results from LDST; independent variable: ACB score; covariables included in the regression model: sex, age, education standard (casmin3_2: comparison between medium and low educational standard; casmin3_3: comparison between high and low educational standard), income, number of diseases weight by severity, used FORTA drugs.
.FORTA, Fit for the Aged; LDST, letter digit substitution test.

one hand, alternative treatments are partly not available or appropriate, and on the other hand, there are risk of anticholinergic side effects. That is why we need to weigh the risk between deprescribing and a possible undertreatment of critical conditions. Consequently, we are in need to develop interdisciplinary processes for deprescribing. Ailabouni *et al* invented a five-step systematic intervention in deprescribing anticholinergic and sedative drugs for a small patient collective. Although they could not report an improvement in cognitive function over a time period of 6 months after deprescribing, they could lower the used medication in mean about 2.1 drugs per patient. They also detected that patients reported significantly less adverse effects, reduced frailty and falls.[45] However, for deprescribing, we are in need for validated tools, with regard to anticholinergic drug use and regarding potentially inappropriate medication. In addition, it is interesting to know whether it is necessary to evaluate patients' medication concerning PIM lists and anticholinergic burden lists. Studies revealed a high proportion of anticholinergics and sedatives within the detected PIM, but there was no analysis with regard to the necessity of using PIM tools and tools to evaluate the anticholinergic burden.[46] Although we determined by including FORTA PIM into the regression model a decrease of the regression coefficient for ADS and German ACB score about −0.1, the anticholinergic scores and therefore the use of anticholinergic drugs according to ADS and German ACB score still seemed to have a negative influence on the cognitive function on multimorbid elderly patients. In addition, the FORTA list did not cover all drugs detected with ADS and/or German ACB score. So, we assume that multimorbid elderly patients could benefit from the use of both lists (PIM and anticholinergic burden).

Strength and limitations

Our study has some strengths and limitations. Unfortunately, we could not underline our results by showing an impact of anticholinergic drug use on peripheral anticholinergic ADR (eg, dry mouth, blurred vision, constipation, nausea, urinary retention, impaired sweating or

tachycardia) because such parameters were not gained during data collection. However, other studies showed that anticholinergic drug use is associated with significantly increased mouth dryness.[31]

Most studies had a less healthy patient collective than we had, due to the fact that we excluded patients living in nursing homes. De Vreese *et al*[4] detected that especially patients from nursing homes are at a greater risk of receiving anticholinergic drugs. However, we could demonstrate that even the apparently more healthy elderly patients are in great risk for receiving anticholinergic drugs and thereby suffering from anticholinergic side effects in association with decreased cognitive function. Moreover, we could not evaluate the length of intake of anticholinergic drugs. Further studies, especially longitudinal studies, are necessary to evaluate the decrease in cognitive function over time. As cognitive impairments is a complex clinical symptom and the LDST only addresses one single aspect of cognition, further tests would help to underline our findings. However, a strength of our study is that we performed a multivariate analysis, including among other number of diseases weighted by severity. A sensitivity analysis was performed, revealing that FORTA PIM has to be included as a confounder in the regression model. In contrast to the number of used drugs, which had no significant influence on the results in LDST (ADS score: p=0.257, regression coefficient: −0.04; ACB score: p=0.518; regression coefficient: −0.02). An additional strength is also the advanced treating of missing values via hot deck imputation.

Taken together, anticholinergic drugs and drugs with anticholinergic activity in multimorbid elderly adults appear to be associated with harms that, in certain circumstances, outweigh their potential benefit. We could determine that a high anticholinergic score is associated with a reduced cognitive function, according to increased poorer results in LDST, in multimorbid elderly patients. In addition, we showed that especially drugs with low anticholinergic risk, for example, for treating cardiovascular conditions, contribute to the anticholinergic burden.

CONCLUSION

Our study demonstrated that it is important to gain greater awareness for the risk of using anticholinergic drugs in multimorbid elderly patients and that there exist tools that are easy to use in medical routine to calculate the anticholinergic burden of this vulnerable patient group. Furthermore, we pointed out that the newly invented German ACB score by Kiesel *et al* seems to generate comparable results with already validated and established tools. However, it needs to be validated in future in order to gain data about the safe use of this tool.

As shown in our study, it is also important to question lower potential anticholinergic drugs, since cumulative effects of those low potential anticholinergic drugs can lead to high anticholinergic burdens as well.

Further studies are needed, especially showing the effect on patient outcome on deprescribing anticholinergic drugs over a longer time period and longitudinal studies to demonstrate the development of cognitive function under use of anticholinergic drugs over time.

In summary, a high anticholinergic burden and therefore anticholinergic drug use is associated with a decreased cognitive function in multimorbid elderly patients. In order to contribute to an improvement in drug therapy safety, we need to invent strategies for rational prescribing and deprescribing.

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4. Zusammenfassung

Im Rahmen dieser Promotionsarbeit konnte anhand der Daten der MultiCare Studie gezeigt werden, dass die Arzneimitteltherapie von multimorbiden, älteren Patienten (3189, 59,3 % Frauen) sehr vielschichtig ist. Die MultiCare Studie bietet ein ideales Studienkollektiv, um Arzneimittel zu charakterisieren, PIM (mittels FORTA-, PRISCUS- und EU(7)-PIM-Liste) und Anticholinergika (mittels ADS- und deutschen ACB-Score) zu identifizieren und deren Einfluss auf die kognitive Funktion der multimorbiden, älteren Patienten (mittels „Letter Digit Substitution Test“) zu bestimmen, da unter anderem neben verschreibungspflichtigen Arzneistoffen auch OTC-Arzneistoffe oder Substanzen im „Brown-Bag“ Verfahren erfasst wurden. Die mittels explorativer Faktorenanalyse gefundenen nicht-zufälligen Verordnungsmuster in der Arzneimitteltherapie geben Hinweise auf gängige Krankheitsbilder. Weiterhin sind Assoziationen mit den durch Schäfer et al. publizierten Morbiditätsclustern zu erkennen. Die Verordnungsmuster und die hohe Anzahl an gefunden Arzneistoffen pro Patient (Mittelwert: 7,7 Arzneistoffe) geben Hinweise auf Multimedikation. Dabei ist auch die Art der eingenommenen Arzneistoffe von Bedeutung, da gerade im Alter das Risiko für die Einnahme von potentiell inadäquater Medikation oder Arzneistoffen mit anticholinergen Nebenwirkungen erhöht ist. Es konnte gezeigt werden, dass die drei PIM-Listen, FORTA (absolut: 2152, Mittelwert: 0,9 ± 1,0 PIM pro Patient), PRISCUS (936, 0,3 ± 0,6) und EU(7)-PIM-Liste (4311, 1,4 ± 1,3), die Arzneimittel unterschiedlich bewerteten und die detektierten PIM eine zum Teil hohe Heterogenität aufwiesen. Mittels multivariater linearer Regression konnte eine Assoziation zwischen PIM Einnahme und einer Abnahme der kognitiven Fähigkeiten beobachtet werden. Dies zeigte sich besonders stark für die durch FORTA detektierten PIM. Mittels Untersuchungen zu Arzneistoffen mit anticholinergen Nebenwirkungen konnte gezeigt werden, dass der deutsche noch nicht validierte ACB-Score (absolut: 2750, Mittelwert: 1,2 ± 1,6) vergleichbare Ergebnisse liefert, wie der weltweit etablierte ADS-Score (1764, 0,8 ± 1,3). Arzneistoffe mit niedriger individueller Last (Score von 1) und Arzneistoffe aus der kardiovaskulären Hauptgruppe bergen hierbei ein besonders großes Risiko. Mit Hilfe von multivariater linearer Regression konnten beide Scores mit einem negativen Effekt auf die kognitiven Fähigkeiten der multimorbiden älteren Patienten assoziiert werden.

Zusammenfassend konnte festgestellt werden, dass die Arzneimitteltherapiesicherheit der multimorbiden Patienten durch das Risiko von Multimedikation, der Einnahme von potentiell inadäquater Medikation und Anticholinergika gefährdet ist.

5. Summary

This doctoral thesis showed, using MultiCare data, that the drug therapy of multimorbid, elderly patients (3,189, 59.3% women) is highly complex. MultiCare study collected data about prescription drugs and OTC drugs that were recorded using brown-bag procedure. Therefore, MultiCare offers an ideal study collective to characterize the drug use of multimorbid elderly patients, in order to identify PIM (using FORTA, PRISCUS and EU(7)-PIM list) and anticholinergic drugs or drugs with anticholinergic side effects (using ADS and German ACB-Score) and their influence on the cognitive function (using the letter digit substitution test) of those patients. This thesis displayed that the detected non-random drug patterns (exploratory factor analysis) for men and women showed a relation in drug use and provides information on common clinical pictures. Furthermore, there are associations with morbidity clusters published by Schäfer et al. The overlap of the drug patterns and the high number of drugs detected per patient (mean: 7.7 drugs) indicated multimedication. Moreover, the type of detected drugs plays an important role in the drug therapy safety of multimorbid elderly patients. The study revealed that the three PIM lists, FORTA (absolute: 2152, mean 0,.9 ± 1.0 PIM per patient), PRISCUS (936, 0.3 ± 0.6) and EU(7)-PIM list (4311, 1.4 ± 1.3), rated drugs differently and the detected PIM showed a broad heterogeneity. By using multivariate linear regression, associations between PIM use, according to all three lists, and a decreased cognitive function was detected. This effect was especially apparent for PIM identified using the FORTA list. The study revealed that the use of drugs with anticholinergic side effects can have a major impact on medication safety. The German ACB score (absolute: 2750, mean: 1.2 ± 1.6) and the worldwide well-established ADS score (1764, 0.8 ± 1.3) provided comparable results. In particular, the cumulative use of anticholinergic drugs with only low (Score 1) anticholinergic potential and especially from the cardiovascular main group poses a major risk for multimorbid elderly patients. The existing examined PIM lists and anticholinergic scores are good tools to improve the drug therapy safety of multimorbid elderly patients in the clinical routine or in primary care if used correctly.

Taken together, the medication safety of multimorbid elderly patients is at risk because those patients are highly in danger of being exposed to multimedication, using potentially inappropriate medication and drugs with anticholinergic side effects. So we need to focus on an adequate drug therapy for those highly vulnerable patients in order to improve the medication safety of multimorbid elderly patients.

6. Erklärung des Eigenanteils an den Publikationen

Ich habe die Doktorarbeit in der Klinikapotheke des Universitätsklinikums Hamburg-Eppendorf im Rahmen des PhD-Programms für Nicht-Mediziner, unter der Betreuung von Frau PD Dr. Claudia Langebrake durchgeführt.

Die Idee zur Studie sowie der erste Studienentwurf wurden von Frau PD Dr. Claudia Langebrake und mir gemeinsam entwickelt. An der Weiterentwicklung bis zum fertigen Studienentwurf haben zusätzlich noch meine beiden weiteren Betreuer Prof. Dr. Martin Scherer und Prof. Dr. Wolfgang von Renteln-Kruse und Dr. Ingmar Schäfer mitgewirkt.

Die Grundlage für die durchgeführten Analysen bilden die Daten der MultiCare Studie, die mir freundlicherweise von Prof. Martin Scherer als Vertreter des MultiCare Konsortiums zur Verfügung gestellt wurden.

Die statistischen Analysen, sowohl die explorative Faktorenanalyse als auch die multivariaten linearen Regressionen zur Ermittlung der Assoziation zwischen der PIM Einnahme bzw. der anticholinergen Last und der kognitiven Funktion gemäß LDST erfolgte in Zusammenarbeit mit Dr. Ingmar Schäfer. Alle weiteren Analysen und Auswertungen wurden von mir durchgeführt.

Die Manuskripte für die eingeschlossenen Publikationen sowie die verwendeten Abbildungen und Tabellen wurden durch mich verfasst und erstellt. Ebenfalls wurde die zusammenfassende Darstellung der Publikationen im Rahmen der Synopse durch mich erstellt.

7. Danksagung

An dieser Stelle, möchte ich den nachstehenden Personen, die mir die Erstellung meiner Dissertation ermöglicht haben, meinen Dank aussprechen.

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8. Lebenslauf

„Lebenslauf wurde aus datenschutzrechtlichen Gründen entfernt“

9. Eidesstattliche Versicherung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.

Ferner versichere ich, dass ich die Dissertation bisher nicht einem Fachvertreter an einer anderen Hochschule zur Überprüfung vorgelegt oder mich anderweitig um Zulassung zur Promotion beworben habe.

Ich erkläre mich einverstanden, dass meine Dissertation vom Dekanat der Medizinischen Fakultät mit einer gängigen Software zur Erkennung von Plagiaten überprüft werden kann.

Unterschrift: .....