Aus dem Institut für Klinische Pharmazie und Toxikologie
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Untersuchung zur Qualität der Schmerzmedikation ambulant betreuter Pflegebedürftiger unter Berücksichtigung von Multimorbidität und Polypharmazie in Deutschland
Analysis of the quality of pain medication in patients receiving home care considering multimorbidity and polypharmacy in Germany

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von

Juliana Schneider

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1 Abstrakt (Deutsche Version)

Hintergrund: Ältere Menschen sind oft von einer hohen Komorbiditätslast betroffen, die im Alter mit Schmerzen assoziiert sein kann. Trotz vielfacher Polypharmazie sind chronische Schmerzpatienten oft mit Schmerzmitteln unterversorgt. Für die ambulante Versorgung Pflegebedürftiger in Deutschland fehlen zuverlässige Daten zur Schmerzsituation sowie zur Angemessenheit der Schmerzmedikation. Ziel dieser Arbeit war es somit, das Schmerzgeschehen älterer Pflegebedürftiger in diesem Setting zu erfassen und deren Pharmakotherapie auszuwerten.

Methodik: Im Rahmen der Querschnittstudie *ACHE* wurden in strukturierten Interviews Daten zum Schmerzgeschehen bei älteren Pflegebedürftigen (Alter ≥ 65 Jahre) mit chronischen Schmerzen (mit oder ohne kognitive Einschränkungen) in der eigenen Häuslichkeit erhoben. Angaben zur Schmerzintensität wurden unter Nutzung des *Brief Pain Inventory* (BPI-NHR) erfasst. Qualität und Angemessenheit der ärztlichen Schmerzmedikation wurden mittels deutschsprachiger *Pain Medication Appropriateness Scale* ($PMAS_D$) bewertet. Ein PMAS-Score (S_{PMAS}) ≤ 67% weist auf eine inadäquate Schmerztherapie hin. Die individuelle Komorbiditätslast wurde mit dem Charlson-Comorbidity-Index (CCI) ermittelt. Unter Berücksichtigung von ärztlich verschriebenen und in der Selbstmedikation bezogenen Arzneistoffen wurde die Gesamtmedikation im Hinblick auf Polypharmazie (≥ 5 Arzneistoffe), klinisch relevanten Arzneimittelinteraktionen sowie Über- und Unterversorgung mit bestimmten Arzneistoffklassen ausgewertet.

Ergebnisse: In die *ACHE*-Studie wurden insgesamt 355 Pflegebedürftige eingeschlossen. Die Pflegebedürftigen (n = 225) berichteten eine hohe Schmerzbelastung mit einer durchschnittlichen Schmerzintensität von 5,3 ± 2,0 in den letzten 24 Stunden. Von 322 Pflegebedürftigen erhielten 58 (18,0%) Pflegebedürftige eine angemessene Schmerzmedikation. Der mediane S_{PMAS} lag bei 47,6% (Bereich 0 - 100%). Bei mehr als der Hälfte (55,4%) von 334 Pflegebedürftigen wurde eine moderate bis hohe Komorbiditätslast ermittelt. Der Median für die Anzahl der verschriebenen Arzneistoffe lag bei 9 (Bereich 0 - 25). Insgesamt waren 89,5% von 353 Pflegebedürftigen von Polypharmazie (≥ 5 verschriebene Arzneistoffe) betroffen, während bei 49,3% Multipharmazie (≥ 10 verschriebene Arzneistoffe) vorlag. Bei 15,5% der

Pflegebedürftigen wurde eine Überversorgung mit Schleifendiuretika ohne angemessene Indikation festgestellt, während bei 32,3% der Pflegebedürftigen mit Vorhofflimmern eine Unterversorgung mit Antikoagulantien beobachtet wurde.

Diskussion: Die vorliegende Arbeit deckt erhebliche Defizite in Qualität und Angemessenheit des pharmakologischen Schmerzmanagements sowie der allgemeinen Pharmakotherapie bei älteren, multimorbiden Pflegebedürftigen (mit oder ohne kognitiven Einschränkungen) bei hoher Schmerzbelastung auf. Es besteht ein dringender Bedarf für interdisziplinäre Versorgungskonzepte in der häuslichen Schmerzversorgung von älteren Pflegebedürftigen.

2 Abstract (English Version)

Background: Older adults are often affected by a high burden of comorbidity, which could be associated with pain. Despite high prevalence of polypharmacy, chronic pain patients are often undertreated with analgesics. In Germany, there is a lack of data concerning pain management and appropriateness of pain medication of elderly receiving home care. The aim of this work was to obtain data concerning the pain situation of home care recipients and to assess the overall medication in this setting.

Methods: In the framework of the cross-sectional study *ACHE*, data concerning the pain situation of elderly aged ≥ 65 years with chronic pain (with or without cognitive impairment) were collected during structured interviews. Data on pain intensity was obtained by using the *Brief Pain Inventory* (BPI-NHR). Quality and appropriateness of prescribed pain medication was assessed by the German *Pain Medication Appropriateness Scale* ($PMAS_D$). A PMAS-score (S_{PMAS}) ≤ 67% indicates an inadequate pain therapy. The individual burden of comorbidities was determined with the Charlson-Comorbidity-Index (CCI). Considering prescribed drugs and drugs used in self-medication, the overall medication was evaluated with regard to polypharmacy (≥ 5 drugs), clinically relevant drug-drug interactions as well as over- and undertreatment with certain drug classes.

Results: In the *ACHE* study, a total of 355 patients in need of care were included. An average pain intensity of 5.3 ± 2.0 in the last 24 h were reported (n = 225). Of 322 patients, 58 patients (18.0%) were adequately treated with pain medication. The median S_{PMAS} was 47.6 % (range 0 - 100%). More than half (55.4%) of 334 patients had moderate to severe comorbidity levels. The median of prescribed medications was 9 (range 0 - 25). Among 353 patients, 89.5% were affected by polypharmacy (≥ 5 prescribed drugs), while in 49.3% of them excessive polypharmacy (≥ 10 prescribed drugs) was detected. Overtreatment with loop diuretics without appropriate indication was determined in 15.5%, while 32.3% of patients with atrial fibrillation were undertreated with anticoagulants.

Discussion: The present work indicates substantial deficits in the quality and appropriateness of pharmacotherapy for pain as well as the overall medication of elderly,

multimorbid patients (with or without cognitive impairment) affected by chronic pain in home care. Interdisciplinary concepts in the ambulatory care of chronic pain patients are required.

3 Zusammenfassung der Publikationspromotion

3.1 Einleitung und Zielstellung

Die globale Lebenserwartung lag 2016 bei 72 Jahren, für Deutschland wurde zum gleichen Zeitpunkt eine Lebenserwartung von über 80 Jahren angegeben [1]. Mit zunehmendem Alter nimmt die Anzahl pflegebedürftiger Menschen zu. In Deutschland waren im Sinne des SGB XI im Dezember 2019 insgesamt 4,1 Millionen Menschen pflegebedürftig; ein Anstieg von 21% im Vergleich zu 2017 [2]. Multimorbidität und Polypharmazie sind in diesem Setting häufig [3, 4]. Es ist bekannt, dass Polypharmazie unerwünschte Arzneimittelwirkungen (UAW), unerwünschte Arzneimittelereignisse (z. B. Stürze, Frakturen) sowie Arzneimittelinteraktionen begünstigt, und besonders im Alter mit einem erhöhten Risiko für Hospitalisierungen und Mortalität assoziiert ist [5, 6]. Mit steigender Anzahl der Arzneimittel nimmt aber - paradoxerweise - auch die Unterversorgung mit Arzneimitteln zu [7]. Darüber hinaus kann es einen Zusammenhang zwischen Multimorbidität und Schmerzen im Alter geben [8-11]. Leiske und Kollegen geben an, dass Pflegeabhängigkeit unter anderem von den Faktoren „Multimorbidität“ und „Schmerzintensität“ beeinflusst wird [12]. In der ambulanten Pflege berichten etwa 70% der Pflegebedürftigen, Schmerzen zu haben [12]. Eine effiziente Schmerztherapie im Alter stellt für den behandelnden Arzt eine Herausforderung dar, weil bei älteren Patienten physiologische Veränderungen, Komorbiditäten und Polypharmazie zu berücksichtigen sind [13]. Chronische Schmerzen sollten nicht als Symptom, sondern als komplexe biopsychosoziale Krankheit verstanden werden [14]. Internationalen Studien zufolge sind chronische Schmerzpatienten trotz zahlreicher Leitlinien oder Handlungsempfehlungen [15-19] oft unterversorgt [20-23]. Gemäß der Ethik-Charta der Deutschen Gesellschaft zum Studium des Schmerzes haben alle Patienten das Recht auf eine ausreichende und individuell angemessene Schmerzversorgung [24]. Die kürzliche Implementierung einer eigenständigen Codierung für „Chronische Schmerzen“ im Rahmen der elften Version der „Internationalen Klassifikation der Krankheiten“ (ICD-11) unterstreicht die Dringlichkeit einer angemessenen Versorgung chronischer Schmerzpatienten [25]. Allerdings fehlen in Deutschland, vor allem für die ambulante Versorgung von Pflegebedürftigen, zuverlässige Daten zur Schmerzsituation sowie zur Schmerzversorgung.

Daher zielte die vorliegende Arbeit darauf ab, das Schmerzgeschehen bei älteren Pflegebedürftigen **(Publikation 1)** [26] zu erfassen sowie die Qualität und

Angemessenheit der ärztlichen Schmerzmedikation in der häuslichen Versorgung in Deutschland **(Publikation 2)** [27] auszuwerten. Um einen umfassenden Einblick in die medikamentöse Versorgung von ambulant betreuten Pflegebedürftigen mit chronischen Schmerzen zu erhalten, wurden weiterhin Ausmaß und Konsequenzen von Polypharmazie einschließlich Über-/Unterversorgung mit Arzneimitteln, Arzneimittel-Interaktionen, als auch die Komorbiditätslast in diesem Setting untersucht **(Publikation 3)** [28].

3.2 Material und Methodik

3.2.1 Studiendesign, Setting und Studienpopulation

Zur Analyse der Fragestellungen wurden Pflegebedürftige mit oder ohne kognitive Beeinträchtigungen, die zu Hause von Pflegediensten oder Angehörigen betreut wurden, rekrutiert. Die Daten wurden infolge der Querschnittstudie *ACHE* („Development of a Model for PAin Management in Older Adults ReCeiving Home CarE“), welche vom GKV-Spitzenverband im Rahmen des Modellvorhabens zur Weiterentwicklung der Pflegeversicherung nach § 8 Abs. 3 SGB XI gefördert wurde [29], im Zeitraum von 09/2017 bis 10/2018 in Berlin erhoben **(Publikation 1, 2, 3)** [26-28]. Einschlusskriterien in die Studie waren: 1) Alter ≥ 65 Jahre, 2) chronische Schmerzbetroffenheit (≥ 3 Monate), 3) Pflegebedürftigkeit nach § 14 Abs. 1 - 2 SGB XI [30] und 4) ambulante Versorgung in der eigenen Häuslichkeit. Der kognitive Status aller eingeschlossenen Pflegebedürftigen wurde mit dem Mini Mental Status Test (MMST) erfasst [31]. Die Studie entspricht den Vorgaben der Deklaration von Helsinki und erhielt von der Ethikkommission der Charité, Universitätsmedizin Berlin, ein positives Votum (EA1/368/14). Eine schriftliche Einverständniserklärung zur freiwilligen Teilnahme an der Studie wurde nach Aufklärung von allen Pflegebedürftigen bzw. von deren gesetzlichen Vertretern im Falle von kognitiver Beeinträchtigung vor jedem Interview eingeholt.

3.2.2 Datenerhebung und Messinstrumente

Der Zugang zu den Pflegebedürftigen wurde überwiegend durch ambulante Pflegedienste in Berlin hergestellt **(Publikation 1, 2, 3)** [26-28].
Die Daten wurden anhand von strukturierten Fragebögen in persönlichen Interviews erhoben [26-28].

Soziodemographische Variablen (z. B. Alter, Geschlecht), Daten zum Pflegegrad, Angaben zum Schmerzgeschehen und zum Schmerzmanagement basieren auf Selbstauskunft, den Informationen pflegender Angehöriger und/oder des Pflegepersonals [26-28].

Ferner wurden Arztbriefe, Entlassungsberichte von Krankenhäusern und/oder Informationen aus der Pflegedokumentation herangezogen, um die vorliegenden chronischen Erkrankungen sowie schmerzbezogenen Diagnosen zu erfassen [26-28]. Der funktionelle Status der Pflegebedürftigen wurde mittels Barthel-Index festgestellt [32]. Die Medikation der Pflegebedürftigen wurde im Rahmen einer erweiterten Medikationsanalyse [33] auf Basis von Arzneimittelpackungen (Brown Bag) und einem persönlichen Gespräch ermittelt [26-28]. Vorliegende Arzneimittelpackungen wurden mithilfe des Instruments zur datenbankgestützten Online-Erfassung von Medikamentendaten (IDOM) [34] unter Nutzung eines Strichcodelesers erfasst [26-28]. Als Datenbasis für IDOM stand die Stammdatei des Wissenschaftlichen Instituts der Ortskrankenkassen (WIdO) unter monatlicher Aktualisierung zur Verfügung [26-28]. Folgende Medikationsdaten wurden per Strichcodeleser gescannt: 1) die Fertigarzneimittel-Bezeichnung, 2) der Arzneistoff, 3) die Dosis, 4) die Darreichungsform, 5) die Applikationsform und 6) die Anatomisch-Therapeutisch-Chemische (ATC) Klassifikation des jeweiligen Arzneistoffs. Zugleich wurden Verordnungsmodus (verordnet, ärztlich empfohlen oder selbst gekauft), Einnahmemodus (regelmäßig, bei Bedarf) und die Dosierung aller Arzneimittel erfragt [26-28]. Arzneistoffe, deren Verordnungsmodus als „ärztlich empfohlen“ angegeben wurde, werden in der vorliegenden Arbeit zu denen vom Arzt verordneten Arzneistoffen gezählt.

Daten zum Schmerzgeschehen **(Publikation 1)** [26] wurden mit dem deutschsprachigen *Brief Pain Inventory* (BPI-NHR) [35] unter Nutzung von vier numerischen Rating-Skalen (NRS) zur Erfassung der Schmerzintensität des geringsten, stärksten und durchschnittlichen Schmerzes in den letzten 24 Stunden sowie des aktuellen Schmerzes erhoben (0 = kein Schmerz, 10 = stärkste vorstellbare Schmerz). In die vorliegende Analyse des Schmerzgeschehens wurden Pflegebedürftige mit einem MMST > 17 [36] eingeschlossen.

Zur Analyse der Qualität und Angemessenheit der verordneten Schmerzmedikation in der ambulanten Versorgung **(Publikation 2)** [27] wurde die aus dem Amerikanischen übersetzte und für Deutschland angepasste *Pain Medication Appropriateness Scale* ($PMAS_D$) eingesetzt [37, 38]. Die $PMAS_D$ wurde bereits zur Analyse des

Schmerzmanagements in Pflegeheimen in Deutschland angewendet und kam auch hier bei Pflegebedürftigen mit kognitiven Beeinträchtigungen zum Einsatz [39].
Die individuelle Komorbiditätslast **(Publikation 3)** [28] wurde mittels Charlson-Komorbiditätsindex (CCI) ausgewertet [40]. Der CCI wurde für den Einsatz in diesem Setting durch das Aufstellen von laienverständlichen Fragen angepasst. Gemäß des CCI lässt sich die Komorbiditätslast wie folgt einteilen: 0 (keine Komorbiditäten), 1 - 2 (gering), 3 - 4 (moderat) und ≥ 5 (hoch) [41]. Neben denen im CCI gelisteten Erkrankungen wurde unter anderem auch nach Hypertonie, koronarer Herzkrankheit (KHK) und Vorhofflimmern (VHF) gefragt [28]. Als in der Literatur häufig beschriebener Cut off-Wert für das Vorhandensein von Multimorbidität [42] wird in der vorliegenden Arbeit die Anzahl von mindestens 2 chronischen Erkrankungen verwendet [28].

3.2.3 Datenanalyse

Zur Analyse des Schmerzgeschehens im Zusammenhang mit der medikamentösen Schmerzmittelversorgung **(Publikation 1)** [26] wurden die vom Arzt verordneten und in der Selbstmedikation bezogenen schmerzreduzierenden Arzneistoffe berücksichtigt.

Zur Analyse der Qualität und Angemessenheit der Schmerzmedikation **(Publikation 2)** [27] wurden nur die ärztlich verordneten, schmerzreduzierenden Arzneistoffe berücksichtigt. Für die Berechnung des finalen $PMAS_D$-Scores (S_{PMAS}) wurden folgende Items berücksichtigt: 1) Medikation bestimmter Schmerzsyndrome, 2) festgelegte Dosierungsintervalle, 3) adäquate Dosierung der Verschreibung im Verhältnis zur Schmerzintensität, 4) Grad der Schmerzlinderung durch verschriebene Medikamente, 5) Prophylaxe bei Obstipation und 6) der Ausschluss risikobehafteter Arzneistoffe für geriatrische Patienten [37, 38]. Der S_{PMAS} ist ein prozentualer Wert, der sich aus erzielten und maximal möglichen Punkten wie folgt zusammensetzt [37, 38]: $S_{PMAS}=\sum(S_{total})/\sum(S_{möglich})*100$. Ein $S_{PMAS} \leq 67\%$ weist auf eine inadäquate Versorgung mit Schmerzmitteln hin [37, 38].
Für die Analyse der Gesamtmedikation **(Publikation 3)** [28] hinsichtlich Polypharmazie (≥ 5 Arzneistoffe), Multipharmazie (≥ 10 Arzneistoffe), dem Vorkommen von Arzneimittelinteraktionen bestimmter Arzneistoffklassen (z. B. Antikoagulantien, Diuretika, Simvastatin) entsprechend Verordnungshäufigkeit und Relevanz in *ACHE* sowie der Über- und Unterversorgung mit Arzneimitteln wurden alle Arzneistoffe berücksichtigt. Ausmaß und Schweregrad relevanter Interaktionen wurden unter Nutzung

des institutionellen Arzneimittelinformationssystems *AiDKlinik*® im Rahmen von Fall-zu-Fall Besprechungen bewertet [28].
Zur Auswertung der Überversorgung mit Arzneimitteln in diesem Setting wurde die Verschreibungsrate der Schleifendiuretika im Hinblick auf eine angemessene Indikation (z. B. Ödeme, Herzinsuffizienz, fortgeschrittene chronische Nierenerkrankung) untersucht [28].
Zur Auswertung der Unterversorgung mit Arzneimitteln wurde die Verordnung von Antikoagulantien bei Pflegebedürftigen mit VHF untersucht [28]. Hierzu wurde das individuelle thromboembolische Risiko über den CHA_2DS_2-VASc (Congestive heart failure/left ventricular dysfunction, Hypertension, Age ≥75 [doubled], Diabetes, Stroke [doubled] – Vascular disease, Age 65-74, and Sex category [female]) Score ermittelt [43].

3.2.4 Statistik

Alle Daten wurden in IBM SPSS Statistics for Windows, Version 25 (IBM Corp, Armonk, NY) ausgewertet. Die Verteilung der Daten wurde mittels Shapiro-Wilk Test geprüft.
Um Gruppenunterschiede zwischen dem stärksten wahrgenommenen Schmerz und den verschiedenen Einnahmemodi (»nur Dauermedikation«, »nur Bedarfsmedikation«, »Dauer- und Bedarfsmedikation«, »keine Medikation«) der Schmerzmedikation (kategorial mit > 2 Gruppen) als auch der Anzahl der schmerzreduzierenden Arzneistoffe (kategorial mit > 2 Gruppen) zu untersuchen, wurden Varianzanalysen („analysis of variance“, kurz: ANOVA), durchgeführt **(Publikation 1)** [26]. Der Einfluss der medikamentösen Schmerzmittelversorgung auf die Intensität des stärksten Schmerzes (abhängige Variable) wurde mittels multipler Regressionsanalyse berechnet [26].
Um Gruppenunterschiede im Rahmen der Analyse zur Qualität und Angemessenheit der ärztlichen Schmerzmedikation **(Publikation 2)** [27] sowie der Analyse der Komorbiditätslast und der Gesamtmedikation (Poly-/Multipharmazie) **(Publikation 3)** [28] zu untersuchen**,** wurde der Mann-Whitney *U* Test (kategorial mit 2 Gruppen) oder Kruskal-Wallis H Test (kategorial mit > 2 Gruppen) mit anschließendem Dunn-Bonferroni Test verwendet. Zur Aufklärung der Zusammenhänge zwischen soziodemographischen Parametern und dem S_{PMAS} [27], Multimorbidität oder Poly-/Multipharmazie [28] wurden Korrelationsanalysen nach Spearman oder der Chi-Quadrat-Test durchgeführt. Um auf einen Unterschied mit Trend zwischen der Anzahl der ärztlichen Gesamtmedikation und den verschiedenen Komorbiditätsleveln (kategorial mit 4 Gruppen) zu prüfen [28], wurde

der Jonckheere-Terpstra Test mit Kendall's tau-b (τ) Korrelationskoeffizienten angewendet.
Für alle Analysen wurde ein p-Wert < 0,05 als statistisch signifikant festgelegt **(Publikation 1, 2, 3)** [26-28].

3.3 Ergebnisse

In die *ACHE*-Studie konnten insgesamt 355 Pflegebedürftige mit chronischen Schmerzen (82,2 ± 7,5 Jahre, 71,5% Frauen) eingeschlossen werden, darunter 22,6% mit schweren kognitiven Beeinträchtigungen (MMST ≤ 17 [36]) **(Publikation 2)** [27]. Knapp die Hälfte (44,8%) der Pflegebedürftigen wiesen Pflegegrad 2 auf [27]. Der mittlere Barthel-Index lag bei 66,7 ± 27,5 [27].

3.3.1 Analyse des Schmerzgeschehens

Für die Auswertung des Schmerzgeschehens mittels BPI-NHR [35] konnten die Daten von 225 (63,4%) auskunftsfähigen Pflegebedürftigen (81,6 ± 7,5 Jahre, 70,7% Frauen) ausgewertet werden **(Publikation 1)** [26].
Zum Zeitpunkt des Interviews gaben die Betroffenen im Mittel einen Schmerz von 3,8 ± 2,9 auf der NRS an [26]. Für die durchschnittliche Schmerzintensität in den letzten 24 Stunden wurde ein Mittelwert von 5,3 ± 2,0 auf der NRS ermittelt, während für den stärksten Schmerz ein Mittelwert von 7,0 ± 2,2 angegeben wurde [26]. Für den geringsten Schmerz liegt der Mittelwert auf dieser Skala bei 3,0 ± 2,2 [26]. Am häufigsten berichteten die Pflegebedürftigen Kreuzschmerzen (84,4%), Arthrose (73,5%) und neuropathische Schmerzen (61,6%) [26].
In dieser Stichprobe erhielten 25 Pflegebedürftigen (11,1%) trotz im Mittel berichteter stärkster Schmerzen im Bereich von 6,0 ± 2,8 auf der NRS keine Schmerzmittel [26]. Pflegebedürftige mit Schmerzmedikation berichteten im Mittel höhere Intensitätswerte des stärksten Schmerzes als Pflegebedürftige ohne Medikation (nur Dauermedikation M [± SD] 7,5 [1,9], nur Bedarfsmedikation M [± SD] 6,3 [2,2], Dauer- und Bedarfsmedikation M [± SD] 7,3 [1,8], ANOVA, p = 0,001) [26]. Ferner wurde mit steigender Anzahl schmerzreduzierender Arzneistoffe eine signifikant höhere Intensität des stärksten Schmerzen berichtet (ANOVA, p = 0,019). Bei ≥ 4 schmerzreduzierenden Arzneistoffen lag die Intensität des Schmerzes auf der NRS im Mittel bei 7,6 ± 1,3, während Pflegebedürftige mit einem Schmerzmittel eine Intensität des stärksten Schmerzes im

Mittel von 6,6 ± 2,1 berichteten (26). Des Weiteren zeigt die Regressionsanalyse, dass Pflegebedürftige ohne Schmerzmedikation oder nur mit Bedarfsmedikation eine um 1,334 Punkten (Regressionsanalyse, p = 0,004) bzw. um 1,052 Punkten (Regressionsanalyse, p = 0,001) reduzierte Schmerzintensität auf der NRS berichteten [26]. Darüber hinaus geht aus dem finalen Regressionsmodell hervor, dass die Einnahmemodi »nur Dauermedikation« sowie »Dauer- und Bedarfsmedikation« keinen Einfluss auf die Reduktion der Schmerzintensität hatten [26].

3.3.2 Analyse der Qualität und Angemessenheit der Schmerzmedikation

Zur Analyse der verschriebenen Schmerzmedikation standen die Daten von 322 (90,7%) Pflegebedürftigen (82,1 ± 7,4 Jahre, 71,4% Frauen) mit chronischen Schmerzen zur Verfügung, darunter 18,9% mit schweren kognitiven Beeinträchtigungen (MMST ≤ 17 [36]) **(Publikation 2)** [27]. Trotz chronischer Schmerzen erhielten 60 (18,6%) Pflegebedürftige keine Schmerzmittel vom Arzt [27]. Bei 81 (25,2%) Pflegebedürftigen wurden Analgetika nur als Dauermedikation vom Arzt verschrieben, während bei 96 (29,9%) Pflegebedürftigen Analgetika lediglich als Bedarfsmedikation verschrieben wurden [27].

Für den S_{PMAS} wurde ein Median von 47,6% (Bereich 0 - 100%) ermittelt [27]. Ein S_{PMAS} > 67% wurde für 58 (18,0%) Pflegebedürftige berechnet [27]. Bei Pflegebedürftigen mit ärztlicher Schmerzmedikation wurden signifikant höhere S_{PMAS}-Werte (Median = 53,3% [Bereich 0 - 100%]) beobachtet als bei Pflegebedürftigen ohne verschriebene Schmerzmedikation (Median = 6,7% [Bereich 0 - 66,7%], Mann-Whitney Test, p < 0,001) [27]. Pflegebedürftige, die ausschließlich Bedarfsmedikation zur Analgesie verordnet bekommen hatten, erzielten einen signifikant geringeren S_{PMAS} als diejenigen mit alleiniger Dauermedikation (Median = 33,3% [Bereich 0 - 100%] vs. 50,0% [Bereich 22,2 - 83,3%], Kruskal-Wallis Test, p < 0,001) [27]. Die höchsten PMAS-Werte wurden für Pflegebedürftige mit Bedarfs- und Dauermedikation (n = 84) festgestellt (Median = 71,4% [Bereich 44,4 - 93,3%], Kruskal-Wallis Test, p < 0,001) [27]. Ein Zusammenhang zwischen S_{PMAS} und Alter, Geschlecht, kognitivem Status, schulischem Abschluss, beruflicher Qualifikation, funktionellem Status oder Schmerzintensität wurde nicht beobachtet [27].

Es wurde eine Korrelation zwischen dem S_{PMAS} und der Anzahl der verschriebenen Schmerzmittel (r_S = 0,672; p < 0,001) gefunden [27]. Bei einem S_{PMAS} ≤ 67% erhielten die

Pflegebedürftigen im Mittel 1,1 ± 0,8 (Bereich 0 - 5) Analgetika, während Pflegebedürftige bei einem S_{PMAS} > 67% im Mittel 2,1 ± 0,8 (Bereich 1 - 4) Analgetika vom Arzt erhalten hatten [27]. Allerdings wurde auch für Pflegebedürftige mit nur einem Analgetikum ein S_{PMAS} > 67% (n = 10/58) ermittelt (Abbildung 1) [27].

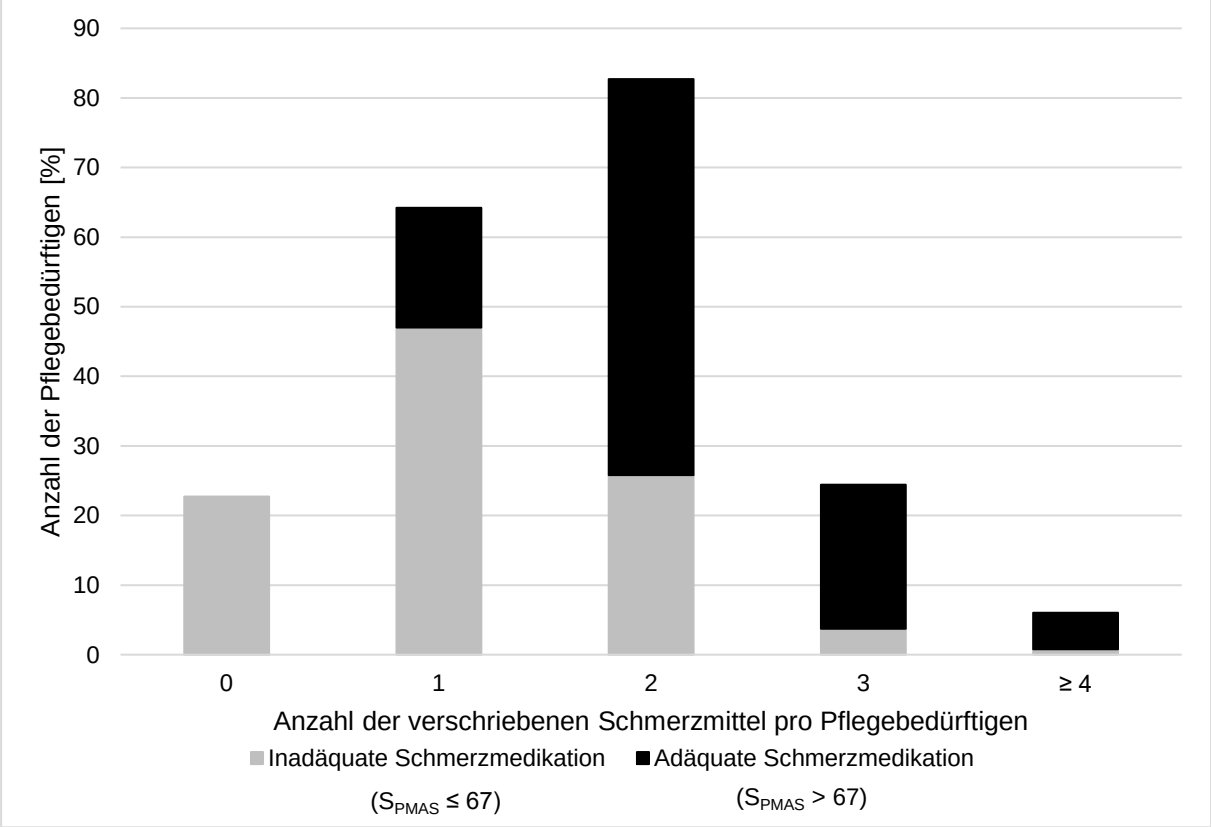

Abbildung 1. Anzahl der verschriebenen Analgetika in Bezug auf die Angemessenheit der Schmerzmedikation.

S_{PMAS}, PMAS-Score; siehe Publikation 2 [27]

Unter den mit Schmerzmitteln therapierten Pflegebedürftigen (n = 262), war Metamizol mit 71,4% das häufigste verordnete Analgetikum (Abbildung 2) [27]. Knapp ein Fünftel (n = 50) der Pflegebedürftigen erhielten systemische nichtsteroidale Antirheumatika (NSAR) und die Hälfte (n = 133) der Pflegebedürftigen wurde mit systemischen Opioiden behandelt [27]. Von den Pflegebedürftigen, die systemische Opioide als Dauermedikation erhalten hatten (n = 118), bekamen lediglich 45,8% eine Obstipationsprophylaxe [27].

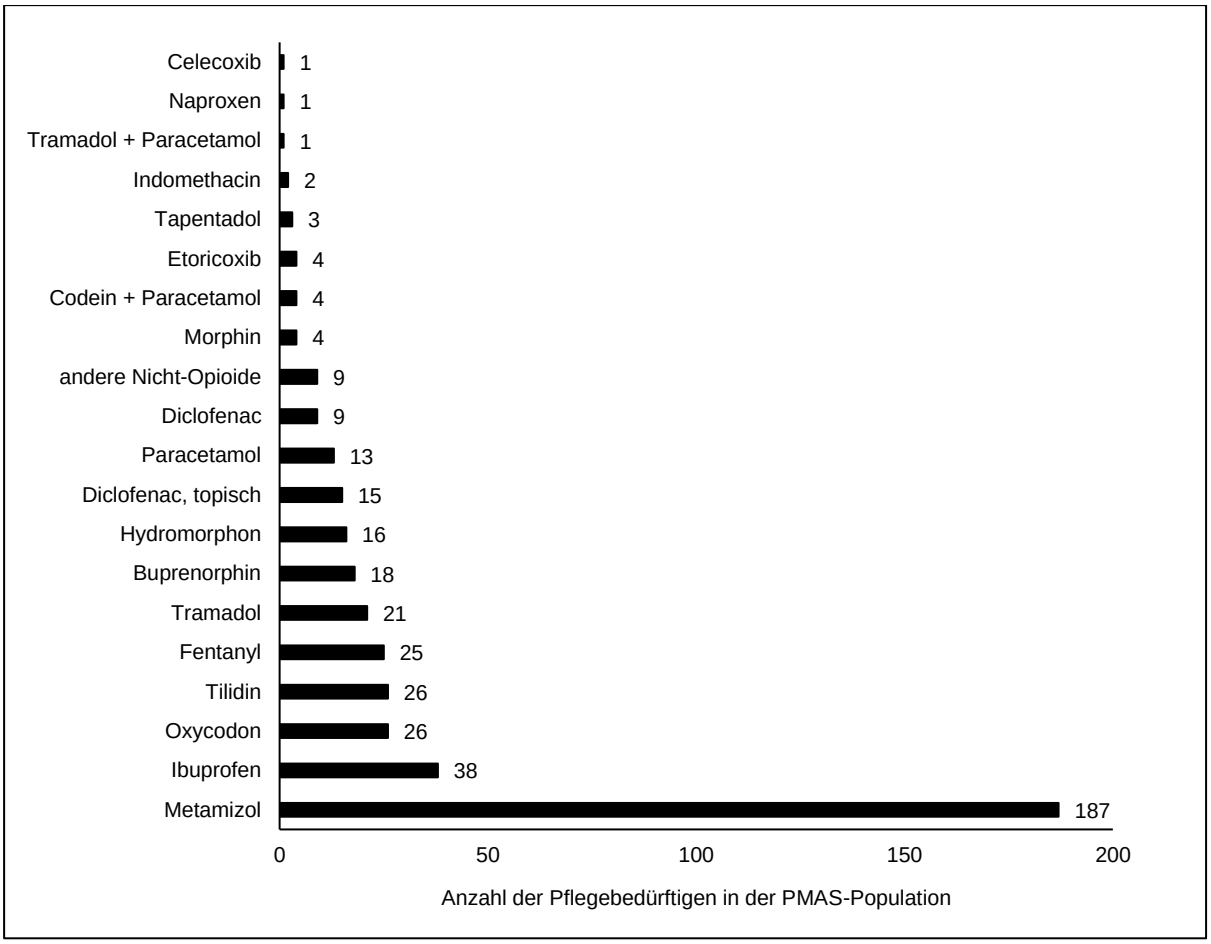

Abbildung 2. Verordnungshäufigkeit der Analgetika in der PMAS-Population.
PMAS, Pain Medication Appropriateness Scale; siehe Publikation 2 [27]

3.3.3 Analyse der Komorbiditätslast

Zur Analyse der individuellen Komorbiditätslast konnten 334 (94,1%) Pflegebedürftige (82,2 ± 7,6 Jahre, 71,6% Frauen) mit chronischen Schmerzen eingeschlossen werden, darunter 19,1% mit schweren kognitiven Beeinträchtigungen (MMST ≤ 17 [36]) **(Publikation 3)** [28]. Die häufigsten Erkrankungen in diesem Setting waren Hypertonie (78,4%), Herzinsuffizienz (41,3%), Diabetes (32,1%), Demenz (27,2%), KHK (26,9%) und chronische Lungenerkrankungen (25,1%) [28]. Für den CCI wurde ein Median von 3 (Bereich 0 - 13) ermittelt [28]. Mehr als die Hälfte der Pflegebedürftigen (55,4%) wiesen eine moderate (35,6%) bis hohe (19,8%) Komorbiditätslast auf [28]. Alter, Geschlecht, Pflegegrad und kognitive Status hatten keinen Einfluss auf die Komorbiditätslast [28]. Multimorbidität (≥ 2 chronische Erkrankungen) im Rahmen des CCI wurde bei 73,7% der Pflegebedürftigen beobachtet. Unter Berücksichtigung weiterer Erkrankungen stieg die Prävalenz für Multimorbidität in diesem Setting auf 91,6% an [28].

3.3.4 Analyse der Gesamtmedikation

Zur Analyse der Gesamtmedikation konnten die Medikationsdaten von 353 (99.4%) Pflegebedürftigen (82,2 ± 7,5 Jahre, 71,7% Frauen) mit chronischen Schmerzen herangezogen werden, darunter 22,7% mit schweren kognitiven Beeinträchtigungen (MMST ≤ 17 [36]) **(Publikation 3)** [28]. Die fünf häufigsten verordneten Arzneistoffklassen waren Analgetika (N02), Diuretika (C03), antithrombotische Mittel (B01), Mittel mit Wirkung auf das Renin-Angiotensin-System (C09) und Mittel bei säurebedingten Erkrankungen (A02) [28]. Der Median für verordnete Arzneistoffe pro Pflegebedürftigen lag bei 9 (Bereich 0 - 25) [28]. Unter Berücksichtigung der Arzneistoffe, die zusätzlich in der Selbstmedikation bezogen wurden, stieg der Median auf 10 (Bereich 0 - 25) an [28]. Insgesamt waren 316 (89,5%) Pflegebedürftige von Polypharmazie (≥ 5 verordnete Arzneistoffe) betroffen, während bei 174/316 (49,3%) Pflegebedürftigen Multipharmazie (≥ 10 verordnete Arzneistoffe) beobachtet wurde [28]. Untersuchungen zu Gruppenvergleichen zeigten, dass Pflegebedürftige mit Polypharmazie oder Multipharmazie signifikant höhere Komorbiditätslevel hatten als Pflegebedürftige ohne Polypharmazie oder Multipharmazie (Mann-Whitney Test, $p < 0,001$) [28]. Ferner gab es einen signifikanten Zusammenhang zwischen der Anzahl der verschriebenen Arzneistoffe und den verschiedenen Komorbiditätsleveln (Kruskal-Wallis Test, $p < 0,001$) (Abbildung 3) [28]. Diesbezüglich konnte ein Unterschied mit positivem Gesamttrend gefunden werden ($\tau = 0,262$, $p < 0,001$) [28]. Es war zu beobachten, dass Polypharmazie als auch Multipharmazie in allen Komorbiditätsleveln auftraten (Abbildung 3) [28].

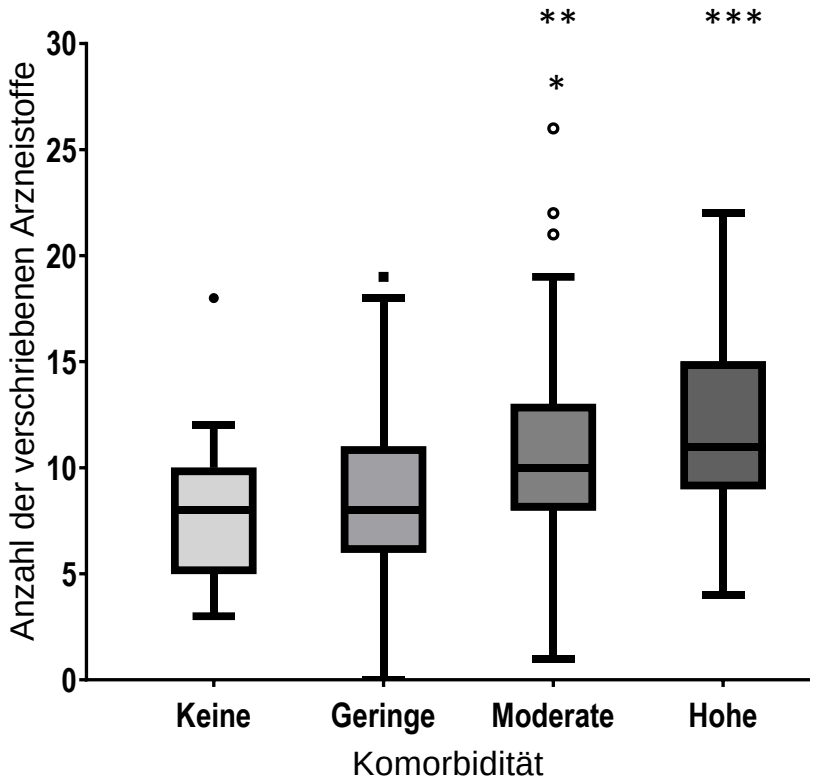

Abbildung 3. Anzahl der verordneten Arzneistoffe gruppiert nach Komorbiditätsleveln. *p < 0.05 vs. keine Komorbidität; **p < 0.01 vs. geringe Komorbidität; ***p < 0.001 vs. geringe Komorbidität; ***p < 0.001 vs. keine Komorbidität; siehe Publikation 3 [28]

Potenziell klinisch relevante Arzneimittelinteraktionen

Insgesamt wurden 184 potenziell klinisch relevante Interaktionen für Antikoagulantien, Diuretika und Simvastatin bei 120/353 (34,0%) Pflegebedürftigen erfasst [28]. Davon wurden 57 (31,0%) Interaktionen als potenziell schwerwiegend eingestuft [28]. Ein Großteil der detektierten Interaktionen entfiel auf Diuretika mit 131 potenziell klinisch relevanten Interaktionen bei 224 Pflegebedürftigen [28]. Für die Antikoagulantien wurden 39 potenziell klinisch relevante Interaktionen bei 80 Pflegebedürftigen identifiziert [28]. Für Simvastatin wurden 17 potenziell klinisch relevante Interaktionen bei 85 Pflegebedürftigen gefunden [28].

Überversorgung mit Arzneimitteln

Insgesamt erhielten 195/334 (59,9%) Pflegebedürftige ein Diuretikum vom Arzt, von denen 174 (89,2%) Pflegebedürftige Schleifendiuretika (Torasemid [n = 160]; Furosemid

[n = 15]) bekamen [28]. Ein Pflegebedürftiger bekam gleichzeitig die beiden Arzneistoffe Torasemid und Furosemid [28]. Bei 11 Pflegebedürftigen wurden Schleifendiuretika mit Thiaziden/Thiazid-Analoga verordnet [28]. Von den Pflegebedürftigen mit Schleifendiuretika hatten 27 (15,5%) keine Indikation für Herzinsuffizienz, fortgeschrittene Nierenerkrankung oder Ödeme [28].

Unterversorgung mit Arzneimitteln

Insgesamt waren 65/334 (19,5%) Pflegebedürftige von VHF betroffen [28]. Für diese Pflegebedürftigen wurde im CHA_2DS_2-VAS Score ein Median von 5 (Bereich 3 - 8) ermittelt [28]. Alle Pflegebedürftigen mit VHF erreichten einen CHA_2DS_2-VAS Score ≥ 2, aber nur 44 (67,7%) Pflegebedürftige erhielten eine Antikoagulation mit Vitamin-K-Antagonisten (VKA) oder direkten oralen Antikoagulantien (DOAK) vom Arzt [28]. Die drei häufigsten Antikoagulantien waren Apixaban (36,4%), Phenprocoumon (29,5%) und Rivaroxaban (20,5%) [28]. Insgesamt wurden 21 (32,3%) Pflegebedürftige nicht antikoaguliert, von denen 19 (90,5%) Pflegebedürftige ≥ 75 Jahre alt waren [28].

3.4 Diskussion

In dieser Arbeit wurden erstmals Daten zum Schmerzgeschehen **(Publikation 1)** [26] von älteren Menschen mit chronischen Schmerzen in der ambulanten Versorgung ausgewertet. Fokus war insbesondere die Qualität und Angemessenheit der ärztlichen Schmerztherapie **(Publikation 2)** [27] sowie Ausmaß und Konsequenzen von Komorbidität und Polypharmazie in diesem Setting **(Publikation 3)** [28].

Die Ergebnisse dieser Untersuchung weisen auf eine hohe Schmerzbelastung unter Pflegbedürftigen mit chronischen Schmerzen in der ambulanten Versorgung hin **(Publikation 1)** [26]. Die in dieser Arbeit berichteten Mittelwerte zur Schmerzintensität (durchschnittlicher Schmerz M [± SD] 5,3 [± 2,0], stärkster Schmerz M [± SD] 7,0 [± 2,2], geringste Schmerz M [± SD] 3,0 [± 2,2]) sind fast doppelt so hoch wie im Pflegeheim (durchschnittlicher Schmerz M [95% CI] 2,5 [1,9 - 3,0], stärkste Schmerz M [95% CI] 4,0 [3,1 - 4,8], geringste Schmerz M [95% CI] 1,6 [1,1 - 2,1]) [44]. Eine kürzlich publizierte polnische Studie, die sowohl Pflegeheimbewohner (n = 97) und ambulante Patienten einer geriatrischen Klinik (n = 48) einschloss, berichtete vergleichbare Mittelwerte für den durchschnittlichen Schmerz im Bereich von 5,3 ± 1,6 auf der NRS, während die Intensität für den stärksten Schmerz im Mittel mit 5,7 ± 1,9 angegeben wurde [45]. Ferner sind eine

hohe Komorbiditätslast sowie eingeschränkte Beweglichkeit Risikofaktoren für multiple Schmerzen [46].

Bei der hohen Schmerzbelastung in diesem Setting wurden erhebliche Defizite im pharmakologischen Schmerzmanagement identifiziert, denn nur 18% der Pflegebedürftigen erhielten eine angemessene Schmerzmedikation vom Arzt (S_{PMAS} > 67% [37]) **(Publikation 2)** [27]. Die defizitäre Schmerzversorgung spiegelt sich zudem im niedrigen Median (S_{PMAS} = 47,6%) in der PMAS wider [27]. Knapp ein Fünftel (18,6%) der Pflegebedürftigen bekamen keine Schmerzmittel [27]. Trotz chronischer Schmerzen in der gesamten Kohorte und der hohen Schmerzintensität in den letzten 24 Stunden, erhielten 29,9% der Pflegebedürftigen entgegen den Empfehlungen einiger Leitlinien [15, 18] Analgetika nur bei Bedarf, während 25,2% der Pflegebedürftigen Analgetika lediglich als Dauermedikation zur Behandlung ihrer Schmerzen vom Arzt verordnet bekommen hatten [27].

Allerdings berichteten Pflegebedürftige mit Schmerzmedikation im Mittel höhere Intensitätswerte des stärksten Schmerzes auf der NRS (nur Dauermedikation M [± SD] 7,5 [1,9], nur Bedarfsmedikation M [± SD] 6,3 [2,2], Dauer- und Bedarfsmedikation M [± SD] 7,3 [1,8], p = 0,001) als Pflegebedürftige ohne Medikation (M [± SD] 6,0 [2,8]) **(Publikation 1)** [26]. Weiterhin geht aus dem finalen Regressionsmodell hervor, dass Pflegebedürftige ohne Schmerzmedikation oder nur mit Bedarfsmedikation signifikant geringere Intensitätswerte des stärksten Schmerzes berichteten als Pflegebedürftige nur mit Dauermedikation oder Dauer- und Bedarfsmedikation [26]. Die Schmerzintensität wurde in den Berechnungen zur Angemessenheit der Schmerzmedikation mittels $PMAS_D$ berücksichtigt **(Publikation 2)** [27], aber es wurde gezeigt, dass keine Korrelation zwischen S_{PMAS} und Schmerzintensität gefunden wurde [27]. Weiterhin wurde eine positive Korrelation zwischen S_{PMAS} und der Anzahl der verordneten Schmerzmittel beobachtet (r_S = 0,672; p < 0,001) [27]. Demgegenüber zeigten die Ergebnisse aus **Publikation 1**, dass mit zunehmender Anzahl schmerzreduzierender Arzneistoffe eine signifikant höhere Intensität des stärksten Schmerzes berichtetet wurde (p = 0,019) [26]. Letztere Beobachtung könnte hierdurch erklärt werden, dass die Angemessenheit der Schmerzmedikation nicht nur von einer hohen Anzahl schmerzreduzierender Arzneistoffe abhängt, sondern auch von der Wahl der Arzneistoffklasse (z. B. Opioide, NSAIDs) in Abhängigkeit des Schmerztyps, die jeweilige Dosis, das Dosierungsintervall als auch die richtige Darreichungsform [37].

Die vorliegenden Ergebnisse zur Unter- bzw. Fehlversorgung mit Schmerzmitteln (»Pflegebedürftige ohne Schmerzmedikation«, »Pflegebedürftige nur mit Bedarfsmedikation» oder »Pflegebedürftige nur mit Dauermedikation») älterer Pflegebedürftiger ähneln internationalen Daten aus Untersuchungen in stationären [21, 23] und ambulanten Settings [20, 47, 48]. Zyczkowska et al. berichteten ebenfalls, dass ein Fünftel der schmerzbetroffenen Pflegebedürftigen in der Häuslichkeit keine Schmerzmedikation erhalten hatten [48]. In der Arbeit von Nawai und Kollegen gaben sogar ein Drittel (31,2%) der in der eigenen Häuslichkeit lebenden Älteren mit moderaten bis starken Schmerzen an, keine Schmerzmittel zu beziehen [20].

Vergleichbare Daten zum defizitären pharmakologischen Schmerzmanagement veröffentlichte eine Pflegeheimstudie in Deutschland [39]. In dieser Studie waren nur 24% der von chronischen Schmerzen betroffenen Heimbewohner angemessen versorgt [38, 39].

Ältere, multimorbide Patienten werden oft von Untersuchungen des Schmerzgeschehens ausgeschlossen [13, 49, 50]. Darüber hinaus stellen kognitive Beeinträchtigungen oder Demenz häufig ein Ausschlusskriterium dar [20, 21, 23, 51]. In die vorliegenden Analysen zur Qualität und Angemessenheit der Schmerzmedikation, der Komorbiditätslast als auch der Gesamtmedikation wurden Pflegebedürftige mit funktionellen als auch schweren kognitiven Beeinträchtigungen sowie einer hohen Komorbiditätslast eingeschlossen **(Publikation 2, 3)** [27, 28].

Mehr als die Hälfte (55,4%) der Pflegebedürftigen weisen eine moderate bis hohe Komorbiditätslast auf **(Publikation 3)** [28]. Jedoch ist anzunehmen, dass die Pflegebedürftigen dieser Kohorte vermutlich kränker sind, als die vorliegenden Daten es beschreiben. Diese Annahme resultiert aus den kürzlich veröffentlichten Ergebnissen von Wenzel et al. [52]. Im Rahmen dieser Untersuchung wurden erhebliche Defizite in der Pflegedokumentation schmerzbetroffener Pflegebedürftiger in der ambulanten Versorgung identifiziert [52]. Daher wurde für fehlende Diagnosen im CCI null Punkte vergeben. Das heißt, dass zum Beispiel trotz fehlender dokumentierter Diagnose im CCI eine Herzinsuffizienz und/oder mäßig schwere bis schwere Nierenerkrankung beim Pflegebedürftigen vorliegen könnte. Für die Auswertung der Verordnungsrate der Schleifendiuretika könnte dies bedeuten, dass der prozentuale Anteil an Pflegebedürftigen (15,5%) mit einer Verordnung für Schleifendiuretika ohne angemessene Indikation überschätzt werden könnte [28]. Andererseits sind die aufgeführten Ergebnisse ähnlich zu früheren Arbeiten von Kölzsch und Kollegen, wo

27,5% der Pflegeheimbewohner in Deutschland Schleifendiuretika ohne angemessene Indikation erhalten hatten [53]. Die insgesamt hohe Rate verordneter Schleifendiuretika in diesem Setting könnte unter anderem auf die Hypertonie-Prävalenz von 78,4% zurückgehen [28], obwohl nach Empfehlungen der Europäischen Gesellschaft für Kardiologie (ESC) und der Europäischen Gesellschaft für Hypertonie (ESH) zur medizinischen Behandlung der unkomplizierten Hypertonie lediglich Thiazid-/Thiazid-ähnliche Diuretika empfohlen werden [54]. Der Einsatz von Schleifendiuretika ohne angemessene Indikation wird für ältere vulnerable Menschen aufgrund des erhöhten Sturzrisikos als problematisch eingeschätzt [54]. Diuretika, insbesondere Schleifendiuretika, gehören zu den fünf führenden Wirkstoffklassen, deren UAW direkt mit Hospitalisierungen einhergehen [55]. Ältere Menschen sind hier besonders gefährdet, da mit zunehmendem Alter das Risiko für Diuretika-assoziierte Elektrolyt- und Säure-Base-Störungen sowie Hypovolämie steigt [56-58]. Auch der Interaktionscheck in dieser Untersuchung zeigte potenzielle klinisch relevante Interaktionen, die überwiegend Diuretika betreffen und ein engmaschiges Monitoring erfordern [28]. In Anbetracht des hohen Alters und der hohen Komorbiditätslast in diesem Setting wurden einige Interaktionen mit Diuretika als schwerwiegend eingestuft (z.B. Schleifendiuretika/Thiazide – Glykoside, K-sparende Diuretika – ACE-Inhibitoren/Sartane) [28].

Neben der Überversorgung mit Schleifendiuretika wurden in der vorliegenden Arbeit 32,3% (n = 21) der Pflegebedürftigen mit VHF ohne orale Antikoagulation mit Vitamin-K-Antagonisten (VKA) oder direkten oralen Antikoagulantien (DOAK) identifiziert [28]. VHF ist unter den kardiovaskulären Erkrankungen der führende Risikofaktor für einen Schlaganfall [59]. Für Patienten mit VHF wird das relative Risiko für einen Schlaganfall im Alter von 80 bis 89 Jahren mit 4,5% angegeben, während das relative Risiko für Patienten mit Hypertonie oder Herzinsuffizienz im selben Alter bei 1,7% liegt [59]. Alle Pflegebedürftigen mit VHF (n = 65) in diesem Setting erzielten einen CHA_2DS_2-VAS Score ≥ 2, während der Median bei 5 (Bereich 3 - 8) lag [28]. Bei einem CHA_2DS_2-VASc Score ≥ 2 liegt das thromboembolische Risiko bei mindestens 3,7% im Jahr [60]. Ferner empfehlen aktuelle Leitlinien eine orale Antikoagulation mit VKA oder DOAK bei einem CHA_2DS_2-VASc Score ≥ 2 [43]. Trotz der hohen Prävalenz von Poly- und Multipharmazie in der vorliegenden Arbeit waren die Pflegebedürftigen in diesem Setting mit oralen Antikoagulantien unterversorgt [28]. Unterversorgung mit Antikoagulantien wurde bereits in früheren Arbeiten berichtet [61-63].

Die Über- und Unterversorgung mit Arzneimitteln sind ferner ein Hinweis für eine nicht angemessene medizinische Versorgung von pflegebedürftigen Menschen mit chronischen Schmerzen in diesem Setting.

Limitationen

In die vorliegende Arbeit wurden lediglich Pflegebedürftige aus Berlin und nicht aus ganz Deutschland eingeschlossen. Außerdem bestand die Stichprobe aus einer kleinen Anzahl an Pflegebedürftigen, da der Zugang zu dieser vulnerablen Gruppe in der eigenen Häuslichkeit eine Herausforderung darstellte. Daher sind die hier aufgeführten Ergebnisse nicht allgemein auf Deutschland übertragbar. Weiterhin beruhen die Ergebnisse auf einer Momentaufnahme, denn die *ACHE*-Studie wurde als Querschnittstudie konzipiert. Dies bedeutet, dass keine Aussagen zum zeitlichen Verlauf des Schmerzgeschehens möglich waren. Für die Auswertung der Gesamtmedikation heißt das, dass Persistenz von Poly- und Multipharmazie sowie Ausmaß der detektierten potenziell möglichen Arzneimittel-Interaktionen nicht bewertet werden konnte. Somit konnte nicht beurteilt werden, ob ärztliche Korrekturmaßnahmen oder klinische Nachuntersuchungen stattgefunden haben.

Schlussfolgerung

Diese Arbeit präsentiert erstmals Daten und Fakten zur Schmerzsituation in der ambulanten Versorgung in Berlin **(Publikation 1)** [26] und zeigt erhebliche Defizite in Qualität und Angemessenheit des pharmakologischen Schmerzmanagements **(Publikation 2)** [27] sowie der medizinischen Versorgung mit Arzneimitteln von älteren, multimorbiden Pflegebedürftigen (mit oder ohne kognitiven Einschränkungen) mit chronischen Schmerzen **(Publikation 3)** [28].

Vor dem Hintergrund einer hohen Komorbiditätslast sowie medikamentöser Unter- bzw. Fehlversorgung besteht ein dringender Bedarf für interdisziplinäre Versorgungskonzepte in der häuslichen Schmerzversorgung von älteren Pflegebedürftigen. Beim medikamentösen Schmerzmanagment sollte, insbesondere in der ambulanten Versorgung, eine hohe Kommunikationsarbeit zwischen Ärzten/-innen und Pflegepersonal stattfinden [64, 65], aber auch der Einbezug von Apothekern/-innen ist erforderlich [18]. Pflegebedürftige sollten selbst auch als wichtige Akteure mit in die medikamentöse Schmerztherapie einbezogen werden [18].

Die vorliegenden Ergebnisse [26-28] können als Grundlage für die Entwicklung und Testung von Interventionsmaßnahmen in der ambulanten Versorgung dienen, um in diesem Setting die medikamentöse Versorgung inklusive der Schmerzversorgung zu verbessern und die Lebensqualität der Pflegebedürftigen zu steigern.

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4 Eidesstattliche Versicherung

„Ich, Juliana Schneider, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: Untersuchung zur Qualität der Schmerzmedikation ambulant betreuter Pflegebedürftiger unter Berücksichtigung von Multimorbidität und Polypharmazie in Deutschland (Analysis of the quality of pain medication in patients receiving home care considering multimorbidity and polypharmacy in Germany) selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum Unterschrift

5 Anteilserklärung an den erfolgten Publikationen

Juliana Schneider hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1: Dräger D, Kreutz R, Wenzel A, **Schneider J**, Budnick A. Ältere Pflegebedürftige mit chronischen Schmerzen: Querschnittsstudie zur geschlechtsspezifischen Schmerzintensität und Versorgung in der großstädtischen Häuslichkeit. *Der Schmerz.* 2021 Oct;35(5):322-332. doi: 10.1007/s00482-021-00538-5

Beitrag im Einzelnen: Im Rahmen der vorliegenden Arbeit war ich mitverantwortlich für die Rekrutierung von Pflegebedürftigen in der eigenen Häuslichkeit durch Kontaktaufnahme zu ambulanten Pflegediensten, Pflegestützpunkten oder Seniorenwohnanlagen in der Region Berlin. Darüber hinaus entwickelte ich in Zusammenarbeit mit Prof. Dr. med. Reinhold Kreutz eine Checkliste zur Schmerzanamnese, um die Schmerzdiagnosen in unserer Untersuchung strukturiert zu erfassen. Ferner passte ich den Charlson-Comorbidity-Index (CCI) durch das Aufstellen von laienverständlichen Fragen für die Anwendung im ambulanten Setting an. Vor Beginn der Datenerhebung wurden alle Datenerheber*innen zum Umgang mit dem Instrument zur datenbankgeschützten Online-Erfassung von Medikamentendaten (IDOM) von mir geschult. Zudem war ich an der Datenerhebung im kompletten Zeitraum von 09/2017 - 10/2018 beteiligt. Ich führte persönliche Interviews mit den Pflegebedürftigen unter Nutzung strukturierter Fragebögen durch. Während der Datenerhebung war ich für die monatliche Aktualisierung der IDOM-Datenbasis durch das Einspielen der aktualisierten Stammdatei des Wissenschaftlichen Instituts der Ortskrankenkassen (WIdO) verantwortlich. Nach Beendigung der Datenerhebung war ich für die Aufbereitung und Bereinigung der Daten zum pharmakologischen Schmerzmanagement (z. B. Schmerzmedikationsverordnung, Anzahl Schmerzmittel/Arzneistoffe), zu den Schmerzdiagnosen und den Daten zur Komorbidität verantwortlich, die in die Berechnungen dieser Publikation eingeflossen sind. Am Manuskript, welches maßgeblich durch Frau PD Dr. Dagmar Dräger erstellt wurde, beteiligte ich mich durch konstruktive Hinweise und Beratung hinsichtlich der Interpretation und Darstellung pharmazeutischer Daten. Des Weiteren erfolgte meinerseits eine Rückmeldung zur Revision und der Druckfahne des Artikels.

Publikation 2: Schneider J, Algharably E, Budnick D, Wenzel A, Dräger D, Kreutz R. Deficits in pain medication in older adults receiving home care: A cross-sectional study in Germany. *PLoS One*. 2020 Feb;15(2):e0229229. doi: 10.1371/journal.pone.0229229

Beitrag im Einzelnen: Im Rahmen der vorliegenden Arbeit wirkte ich an der Rekrutierung von Pflegebedürftigen und der Erhebung von Daten mit. Die unter Publikation 1 beschriebene Checkliste zur Schmerzanamnese war unter anderem auch für die strukturierte Erfassung der für die Pain Medication Appropriateness Scale ($PMAS_D$) erforderlichen Schmerzdiagnosen relevant. Die Angemessenheit der verordneten Schmerzmedikation von ambulant versorgten Pflegebedürftigen wurde eigenständig von mir unter Anwendung der $PMAS_D$ ausgewertet. Die Aufbereitung der erforderlichen Daten führte ich in SPSS 25 durch. Bei der Auswertung des pharmakologischen Schmerzmanagements berücksichtigte ich die verordneten Schmerzmittel im Zusammenhang mit Dosis und Dosisintervall individuell auf Basis zugrunde liegender Schmerzdiagnosen. Alle in der vorliegenden Arbeit beschriebenen statistischen Analysen wurden ebenfalls eigenständig von mir durchgeführt. Aus meiner statistischen Auswertung sind alle Tabellen und Abbildungen sowie das zu Publikation 2 zugehörige ergänzende Material entstanden. Des Weiteren war ich hauptverantwortlich für die Erstellung des ersten Artikelentwurfs. Relevanz und Bedeutung der Ergebnisse wurden von mir nach ausführlicher Literaturrecherche diskutiert. Kritisches Feedback zu den Inhalten des Manuskripts erhielt ich von Prof. Dr. med. Reinhold Kreutz, Ph.D Engi Abd Elhady Algharably, PD Dr. Dagmar Dräger, Dr. rer. medic. Andrea Budnick und Dipl.-Med.-Päd. Arlett Wenzel. Ferner war ich als Erstautorin für die Einreichung bei „PLoS One“ verantwortlich, bearbeitete federführend die Revision und war zudem Ansprechpartnerin für alle Interaktionen mit dem Journal.

Publikation 3: Schneider J, Algharably EAE, Budnick A, Wenzel A, Dräger D, Kreutz R. High prevalence of multimorbidity and polypharmacy in elderly patients with chronic pain receiving home care are associated with multiple medication-related problems. *Frontiers in Pharmacology*. 2021 Jun;12:686990. doi: 10.3389/fphar.2021.686990

Beitrag im Einzelnen: Im Rahmen der vorliegenden Arbeit war ich an der Rekrutierung von Pflegebedürftigen über Berliner Pflegedienste und der Datenerhebung beteiligt. Als wissenschaftliches Instrument zur Auswertung der individuellen Komorbiditätslast von Pflegebedürftigen in der ambulanten Versorgung nutzte ich den CCI. Weiterhin wertete ich Ausmaß und Konsequenzen von Polypharmazie

einschließlich Über-/Unterversorgung von Arzneimitteln in diesem vulnerablen Setting aus. Die Aufbereitung der erforderlichen Daten führte ich in SPSS 25 durch. Das Ausmaß von Polypharmazie wertete ich eigenständig mittels deskriptiver Statistik aus. Als Konsequenz von Polypharmazie prüfte ich das Vorkommen von Interaktionen relevanter Arzneistoffklassen (z. B. Antikoagulantien, Diuretika, Simvastatin) in diesem Setting. Ausmaß und Schweregrad der Interaktionen bewertete ich im Zuge von Fall-zu-Fall Besprechungen in wissenschaftlicher Diskussion mit Prof. Dr. med. Reinhold Kreutz und Ph.D Engi Abd Elhady Algharably. Zur Auswertung der Überversorgung mit Arzneimitteln untersuchte ich die Verordnungsrate von Schleifendiuretika im Hinblick auf angemessene Indikation wie beispielsweise Ödeme, Herzinsuffizienz oder fortgeschrittene chronische Nierenerkrankung. Um die Fragestellung auf Unterversorgung mit Arzneistoffen zu beantworten, prüfte ich die Verordnung von oralen Antikoagulantien bei Pflegebedürftigen mit Vorhofflimmern unter Berücksichtigung des individuellen thromboembolischen Risikos über den CHA_2DS_2-VASc (Congestive heart failure/left ventricular dysfunction, Hypertension, Age ≥75 [doubled], Diabetes, Stroke [doubled] – Vascular disease, Age 65-74, and Sex category [female]) Score. Aus meiner statistischen Auswertung resultieren alle Tabellen und Abbildungen sowie das zu Publikation 3 zugehörige ergänzende Material. Ich übernahm die Federführung bei der Erstellung des ersten Artikelentwurfs. Der wissenschaftliche Hintergrund, die Beschreibung der angewendeten Methodik, die Präsentation der Ergebnisse und die Diskussion wurden eigenständig von mir unter Berücksichtigung aktueller Literatur verfasst. Konstruktive Vorschläge zum Manuskript erhielt ich von Prof. Dr. med. Reinhold Kreutz, Ph.D Engi Abd Elhady Algharably, PD Dr. Dagmar Dräger, Dr. rer. medic. Andrea Budnick und Dipl.-Med.-Päd. Arlett Wenzel. Ich übernahm als Erstautorin den Einreichungsprozess bei „Frontiers in Pharmacology“ und war zudem verantwortlich für die Revision vom Journal. Ferner war ich Ansprechpartnerin für alle Interaktionen mit „Frontiers of Pharmacology“.

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Unterschrift, Datum und Stempel des/der erstbetreuenden Hochschullehrers/in

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Unterschrift des Doktoranden/der Doktorandin

6 Auszüge aus der *Journal Summary List* (ISI Web of Knowledge^{SM})

6.1 **Publikation 1:** Dräger D, Kreutz R, Wenzel A, Schneider J, Budnick A. Ältere Pflegebedürftige mit chronischen Schmerzen: Querschnittsstudie zur geschlechtsspezifischen Schmerzintensität und Versorgung in der großstädtischen Häuslichkeit. *Der Schmerz*. 2021 Oct;35(5):322-332.

Journal Data Filtered By: **Selected JCR Year: 2018** Selected Editions: SCIE,SSCI Selected Categories: **"CLINICAL NEUROLOGY"** Selected Category Scheme: WoS
Gesamtanzahl: 199 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	LANCET NEUROLOGY	30,748	28.755	0.069460
2	Nature Reviews Neurology	9,548	21.155	0.031060
3	ACTA NEUROPATHOLOGICA	20,206	18.174	0.041660
4	Alzheimers & Dementia	13,341	14.423	0.036340
5	JAMA Neurology	8,683	12.321	0.042040
6	BRAIN	52,970	11.814	0.074030
7	SLEEP MEDICINE REVIEWS	6,920	10.517	0.010920
8	NEURO-ONCOLOGY	11,858	10.091	0.029150
9	ANNALS OF NEUROLOGY	37,336	9.496	0.048630
10	NEUROLOGY	89,258	8.689	0.115200
11	JOURNAL OF NEUROLOGY NEUROSURGERY AND PSYCHIATRY	29,660	8.272	0.030730
12	MOVEMENT DISORDERS	26,964	8.061	0.037650
13	Neurology-Neuroimmunology & Neuroinflammation	1,996	7.353	0.008220
14	Brain Stimulation	5,457	6.919	0.014470
15	Epilepsy Currents	799	6.909	0.001560

16	NEUROPATHOLOGY AND APPLIED NEUROBIOLOGY	3,876	6.878	0.006420
17	NEUROSCIENTIST	4,986	6.791	0.008520
18	BRAIN PATHOLOGY	5,263	6.155	0.007880
19	Alzheimers Research & Therapy	3,160	6.142	0.010700
20	STROKE	64,814	6.046	0.082630
21	PAIN	38,312	6.029	0.039070
22	Translational Stroke Research	1,955	5.847	0.004330
23	Multiple Sclerosis Journal	11,501	5.649	0.022750
24	Journal of Stroke	925	5.571	0.003580
25	EPILEPSIA	26,492	5.562	0.033400
26	Neurotherapeutics	4,475	5.552	0.009060
27	JOURNAL OF PAIN	10,405	5.424	0.018280
28	BIPOLAR DISORDERS	5,143	4.936	0.006760
29	Annals of Clinical and Translational Neurology	1,858	4.656	0.008750
30	CURRENT OPINION IN NEUROLOGY	5,290	4.647	0.009650
31	NEUROSURGERY	29,096	4.605	0.020730
32	SLEEP	21,434	4.571	0.024240
33	EUROPEAN NEUROPSYCHOPHARMACOLOGY	7,488	4.468	0.015500
34	International Journal of Stroke	4,172	4.466	0.015210
35	CEPHALALGIA	9,983	4.438	0.014480
36	EUROPEAN JOURNAL OF NEUROLOGY	10,488	4.387	0.016970
37	PARKINSONISM & RELATED DISORDERS	9,119	4.360	0.018810

38	PROGRESS IN NEURO-PSYCHOPHARMACOLOGY & BIOLOGICAL PSYCHIATRY	10,674	4.315	0.012400
39	JOURNAL OF PSYCHOPHARMACOLOGY	6,460	4.221	0.010120
40	INTERNATIONAL JOURNAL OF NEUROPSYCHOPHARMACOLOGY	6,551	4.207	0.012320
41	JOURNAL OF NEUROLOGY	14,910	4.204	0.024550
42	CNS DRUGS	4,602	4.192	0.007190
43	JOURNAL OF NEUROSURGERY	36,001	4.130	0.027880
44	JOURNAL OF AFFECTIVE DISORDERS	30,314	4.084	0.052950
45	CNS SPECTRUMS	2,368	3.940	0.003340
46	JOURNAL OF HEADACHE AND PAIN	3,308	3.918	0.007210
47	NEUROGASTROENTEROLOGY AND MOTILITY	8,314	3.803	0.014510
48	NEUROREHABILITATION AND NEURAL REPAIR	5,071	3.757	0.008480
49	JOURNAL OF NEUROTRAUMA	14,754	3.754	0.019770
50	HEADACHE	7,897	3.749	0.009930
51	CLINICAL NEUROPHYSIOLOGY	19,574	3.675	0.021420
52	Journal of Neurodevelopmental Disorders	1,253	3.590	0.003420
53	Therapeutic Advances in Neurological Disorders	1,148	3.580	0.002760
54	Current Treatment Options in Neurology	1,200	3.574	0.002790
55	DEVELOPMENTAL MEDICINE AND CHILD NEUROLOGY	12,256	3.532	0.013840
56	Brain Tumor Pathology	739	3.509	0.001470
57	PSYCHIATRY AND CLINICAL NEUROSCIENCES	3,720	3.489	0.004230
58	JOURNAL OF NEUROPATHOLOGY AND EXPERIMENTAL NEUROLOGY	9,205	3.460	0.007510
59	Journal of Clinical Sleep Medicine	6,094	3.456	0.011390

60	Expert Review of Neurotherapeutics	4,057	3.453	0.006360
61	JOURNAL OF SLEEP RESEARCH	5,432	3.432	0.007450
62	Current Neurology and Neuroscience Reports	3,004	3.400	0.007210
63	JOURNAL OF PAIN AND SYMPTOM MANAGEMENT	11,229	3.378	0.015750
64	SLEEP MEDICINE	10,218	3.360	0.017130
65	AMERICAN JOURNAL OF NEURORADIOLOGY	23,231	3.256	0.028010
66	Current Alzheimer Research	4,026	3.211	0.005930
67	Spine Journal	9,595	3.196	0.019800
68	EUROPEAN ARCHIVES OF PSYCHIATRY AND CLINICAL NEUROSCIENCE	4,096	3.192	0.004590
69	EUROPEAN JOURNAL OF PAIN	7,263	3.188	0.011070
70	Journal of Neurogastroenterology and Motility	1,407	3.179	0.002950
71	Behavioral Sleep Medicine	1,285	3.171	0.002350
72	JOURNAL OF NEURO-ONCOLOGY	11,487	3.129	0.016820
73	BRAIN TOPOGRAPHY	2,629	3.104	0.004920
74	JOURNAL OF THE INTERNATIONAL NEUROPSYCHOLOGICAL SOCIETY	6,773	3.098	0.007380
75	Nature and Science of Sleep	520	3.054	0.001290
76	NEUROGENETICS	1,268	3.017	0.002320
77	JOURNAL OF NEUROSURGERY-SPINE	7,809	2.998	0.012310
78	JOURNAL OF NEUROSURGICAL ANESTHESIOLOGY	1,495	2.957	0.001710
79	Pain Physician	4,377	2.942	0.007300
80	JOURNAL OF NEURAL TRANSMISSION	6,900	2.903	0.008030
81	SPINE	47,839	2.903	0.033120

82	CLINICAL JOURNAL OF PAIN	6,940	2.893	0.009670
83	Neurosurgical Focus	7,349	2.891	0.010090
84	Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration	3,561	2.883	0.006060
85	Neurocritical Care	4,070	2.857	0.006910
86	ACTA NEUROLOGICA SCANDINAVICA	6,767	2.852	0.007200
87	NEUROLOGIC CLINICS	2,233	2.802	0.003290
88	Clinical Neuroradiology	798	2.800	0.002250
89	Neurodegenerative Diseases	1,560	2.798	0.002450
90	Journal of Clinical Neurology	1,268	2.796	0.002740
91	Current Pain and Headache Reports	2,158	2.767	0.003690
92	SEIZURE-EUROPEAN JOURNAL OF EPILEPSY	5,557	2.765	0.010290
93	JOURNAL OF GERIATRIC PSYCHIATRY AND NEUROLOGY	1,632	2.747	0.001840
94	Multiple Sclerosis and Related Disorders	1,621	2.725	0.005690
95	NEUROEPIDEMIOLOGY	3,266	2.689	0.004980
96	CEREBROVASCULAR DISEASES	5,517	2.681	0.007400
97	JOURNAL OF HEAD TRAUMA REHABILITATION	4,388	2.667	0.005850
98	NEUROMODULATION	2,109	2.663	0.004600
99	JOURNAL OF THE NEUROLOGICAL SCIENCES	17,679	2.651	0.023320
100	Frontiers in Neurology	6,274	2.635	0.019550
101	Journal of Neurologic Physical Therapy	1,022	2.614	0.001550
102	NEUROMUSCULAR DISORDERS	5,164	2.612	0.008560
103	CHILD NEUROPSYCHOLOGY	2,296	2.577	0.002780

104	NEUROSURGERY CLINICS OF NORTH AMERICA	1,637	2.553	0.002420
105	NEUROSURGICAL REVIEW	2,434	2.532	0.002960
106	EUROPEAN SPINE JOURNAL	16,408	2.513	0.021220
107	JOURNAL OF NEURO-OPHTHALMOLOGY	1,748	2.509	0.002520
108	NEURORADIOLOGY	5,656	2.504	0.007020
109	EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY	2,764	2.496	0.005830
110	Pain Practice	2,422	2.486	0.004520
111	CLINICAL AUTONOMIC RESEARCH	1,761	2.485	0.001950
112	NEUROLOGICAL SCIENCES	5,637	2.484	0.009990
113	JOURNAL OF NEURORADIOLOGY	985	2.467	0.001440
114	JOURNAL OF THE PERIPHERAL NERVOUS SYSTEM	1,600	2.441	0.002130
115	MUSCLE & NERVE	12,279	2.393	0.014620
116	ALZHEIMER DISEASE & ASSOCIATED DISORDERS	3,166	2.378	0.003210
116	EPILEPSY & BEHAVIOR	10,335	2.378	0.017530
118	PEDIATRIC NEUROLOGY	5,398	2.326	0.009570
118	Sleep and Breathing	3,128	2.326	0.006070
120	CANADIAN JOURNAL OF NEUROLOGICAL SCIENCES	2,908	2.286	0.003590
121	PSYCHIATRY RESEARCH-NEUROIMAGING	5,503	2.270	0.008330
122	HUMAN PSYCHOPHARMACOLOGY CLINICAL AND EXPERIMENTAL	2,149	2.265	0.002320
123	DEMENTIA AND GERIATRIC COGNITIVE DISORDERS	4,583	2.260	0.003830
124	Journal of Pain Research	2,171	2.236	0.006190
125	BMC Neurology	5,121	2.233	0.012460

126	Neuropsychiatric Disease and Treatment	5,337	2.228	0.012260
127	EPILEPSY RESEARCH	6,815	2.178	0.009800
128	REVUE NEUROLOGIQUE	1,943	2.177	0.002500
129	Journal of Neurosurgery-Pediatrics	4,167	2.170	0.007920
130	NEUROPHYSIOLOGIE CLINIQUE-CLINICAL NEUROPHYSIOLOGY	1,230	2.167	0.001380
131	NEUROPATHOLOGY	1,783	2.161	0.002720
132	JOURNAL OF CHILD NEUROLOGY	6,113	2.092	0.008940
133	JOURNAL OF NEUROIMAGING	2,081	2.080	0.004270
134	OTOLOGY & NEUROTOLOGY	8,094	2.063	0.011170
135	EPILEPTIC DISORDERS	1,305	2.052	0.002400
136	Parkinsons Disease	1,205	2.051	0.002290
137	NEUROLOGIA	1,077	2.038	0.001930
138	CLINICAL NEUROPSYCHOLOGIST	3,186	2.006	0.003220
139	JOURNAL OF CLINICAL AND EXPERIMENTAL NEUROPSYCHOLOGY	5,419	1.994	0.004060
140	NEUROLOGICAL RESEARCH	3,894	1.983	0.003940
141	JOURNAL OF NEUROPSYCHIATRY AND CLINICAL NEUROSCIENCES	3,615	1.971	0.002540
142	BEHAVIOURAL NEUROLOGY	1,340	1.908	0.002430
143	SPINAL CORD	5,874	1.898	0.005740
144	Journal of Neurosurgical Sciences	833	1.883	0.001270
145	JOURNAL OF NERVOUS AND MENTAL DISEASE	8,182	1.859	0.007030
146	ACTA NEUROCHIRURGICA	9,486	1.834	0.009160
147	CLINICAL EEG AND NEUROSCIENCE	1,018	1.822	0.001510

148	CURRENT NEUROVASCULAR RESEARCH	1,044	1.811	0.001370
149	BRAIN & DEVELOPMENT	3,930	1.756	0.004940
150	Clinical Spine Surgery	848	1.726	0.003160
151	World Neurosurgery	10,159	1.723	0.023420
152	JOURNAL OF SPINAL CORD MEDICINE	2,488	1.711	0.003110
153	Pain Research & Management	1,517	1.701	0.002530
154	JOURNAL OF CLINICAL NEUROPHYSIOLOGY	3,076	1.673	0.003540
155	CLINICAL NEUROLOGY AND NEUROSURGERY	5,855	1.672	0.010530
156	APHASIOLOGY	2,862	1.669	0.001970
157	NEUROPEDIATRICS	1,674	1.654	0.002050
158	NEUROLOGIA MEDICO-CHIRURGICA	3,018	1.651	0.002670
159	ACTA NEUROLOGICA BELGICA	991	1.612	0.001670
160	JOURNAL OF CLINICAL NEUROSCIENCE	8,027	1.593	0.013450
161	Korean Journal of Pain	512	1.563	0.000920
162	Applied Neuropsychology-Adult	426	1.548	0.001290
163	Applied Neuropsychology-Child	256	1.528	0.000830
164	Seminars in Pediatric Neurology	1,143	1.506	0.001320
165	BRITISH JOURNAL OF NEUROSURGERY	3,247	1.481	0.003140
166	SEMINARS IN NEUROLOGY	1,761	1.473	0.002650
167	Operative Neurosurgery	632	1.470	0.001450
168	American Journal of Alzheimers Disease and Other Dementias	2,062	1.464	0.002860
169	INTERVENTIONAL NEURORADIOLOGY	1,340	1.450	0.002280

170	Cognitive and Behavioral Neurology	766	1.396	0.000790
171	CHILDS NERVOUS SYSTEM	5,817	1.327	0.006110
172	CLINICAL NEUROPHARMACOLOGY	2,110	1.272	0.001550
173	**SCHMERZ**	**746**	**1.267**	**0.000900**
174	Developmental Neurorehabilitation	835	1.239	0.001590
175	EUROPEAN NEUROLOGY	3,068	1.235	0.003160
176	Journal of Neurological Surgery Part B-Skull Base	669	1.216	0.001690
177	NEUROREHABILITATION	2,546	1.197	0.003990
178	Journal of Korean Neurosurgical Society	1,991	1.187	0.002780
179	NEUROCASE	1,181	1.108	0.001620
180	JOURNAL OF NEUROSCIENCE NURSING	1,071	1.096	0.000970
181	Journal of Neurological Surgery Part A-Central European Neurosurgery	510	1.060	0.001360
182	Neurologia i Neurochirurgia Polska	835	1.006	0.001310
183	Brain Impairment	357	0.958	0.000430
184	NEUROCHIRURGIE	849	0.948	0.000840
185	CLINICAL NEUROPATHOLOGY	917	0.947	0.000860
186	Annals of Indian Academy of Neurology	1,013	0.898	0.001970
187	Turkish Neurosurgery	1,271	0.896	0.001870
188	Neurosciences	504	0.892	0.000760
189	Noropsikiyatri Arsivi-Archives of Neuropsychiatry	377	0.856	0.000740
190	NERVENARZT	1,603	0.829	0.001420
191	NEUROLOGIST	874	0.802	0.000460

192	PEDIATRIC NEUROSURGERY	2,001	0.783	0.000720
193	Sleep and Biological Rhythms	600	0.752	0.000830
194	FORTSCHRITTE DER NEUROLOGIE PSYCHIATRIE	534	0.635	0.000460
195	REVISTA DE NEUROLOGIA	1,755	0.485	0.001080
196	KLINISCHE NEUROPHYSIOLOGIE	40	0.325	0.000030
197	Zeitschrift fur Neuropsychologie	78	0.233	0.000090
198	Neurology Asia	215	0.218	0.000310
199	Ideggyogyaszati Szemle-Clinical Neuroscience	144	0.113	0.000150

Publikation 1: Dräger D, Kreutz R, Wenzel A, Schneider J, Budnick A. Ältere Pflegebedürftige mit chronischen Schmerzen: Querschnittsstudie zur geschlechtsspezifischen Schmerzintensität und Versorgung in der großstädtischen Häuslichkeit. *Der Schmerz*. 2021 Oct;35(5):322-332. https://doi.org/10.1007/s00482-021-00538-5

6.2 **Publikation 2: Schneider J**, Algharably E, Budnick D, Wenzel A, Dräger D, Kreutz R. Deficits in pain medication in older adults receiving home care: A cross-sectional study in Germany. *PLoS One*. 2020 Feb;15(2):e0229229.

Journal Data Filtered By: **Selected JCR Year: 2018** Selected Editions: SCIE,SSCI Selected Categories: **"MULTIDISCIPLINARY SCIENCES"** Selected Category Scheme: WoS
Gesamtanzahl: 69 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	NATURE	745,692	43.070	1.285010
2	SCIENCE	680,994	41.037	1.070190
3	National Science Review	1,842	13.222	0.006500
4	Science Advances	21,901	12.804	0.110010
5	Nature Communications	243,793	11.878	1.103290
6	Nature Human Behaviour	1,230	10.575	0.006550
7	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA	661,118	9.580	1.022190
8	Science Bulletin	3,569	6.277	0.009840
9	Scientific Data	3,240	5.929	0.015610
10	Frontiers in Bioengineering and Biotechnology	1,994	5.122	0.006540
11	Journal of Advanced Research	2,691	5.045	0.004780
12	Research Synthesis Methods	1,932	5.043	0.005420
13	GigaScience	2,674	4.688	0.012510
14	Annals of the New York Academy of Sciences	46,385	4.295	0.025840
15	Scientific Reports	302,086	4.011	1.061540
16	Journal of the Royal Society Interface	12,933	3.224	0.029190

17	NPJ Microgravity	203	3.111	0.000670
18	PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY A-MATHEMATICAL PHYSICAL AND ENGINEERING SCIENCES	19,227	3.093	0.028200
19	FRACTALS-COMPLEX GEOMETRY PATTERNS AND SCALING IN NATURE AND SOCIETY	1,429	2.971	0.001120
20	Journal of Radiation Research and Applied Sciences	860	2.963	0.001860
21	MIT Technology Review	929	2.893	0.001910
22	JOURNAL OF KING SAUD UNIVERSITY SCIENCE	1,120	2.835	0.001670
23	PROCEEDINGS OF THE ROYAL SOCIETY A-MATHEMATICAL PHYSICAL AND ENGINEERING SCIENCES	18,683	2.818	0.018940
24	**PLoS One**	**650,727**	**2.776**	**1.706770**
25	COMPLEXITY	2,753	2.591	0.003890
26	Royal Society Open Science	4,118	2.515	0.017150
27	PeerJ	11,911	2.353	0.045900
28	SCIENCE AND ENGINEERING ETHICS	1,719	2.275	0.003450
29	INTERNATIONAL JOURNAL OF BIFURCATION AND CHAOS	7,008	2.145	0.007390
30	Symmetry-Basel	2,097	2.143	0.002590
31	SCIENTIFIC AMERICAN	6,609	1.946	0.003540
32	Science of Nature	508	1.839	0.002000
33	PROCEEDINGS OF THE JAPAN ACADEMY SERIES B-PHYSICAL AND BIOLOGICAL SCIENCES	1,532	1.833	0.001960
34	Journal of Taibah University for Science	779	1.640	0.001240

PLOS ONE

RESEARCH ARTICLE

Deficits in pain medication in older adults with chronic pain receiving home care: A cross-sectional study in Germany

Juliana Schneider[1], **Engi Algharably**[1], **Andrea Budnick**[2], **Arlett Wenzel**[2], **Dagmar Dräger**[2], **Reinhold Kreutz**[1]*

1 Institute of Clinical Pharmacology and Toxicology, Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany, 2 Institute of Medical Sociology and Rehabilitation Sciences, Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany

* reinhold.kreutz@charite.de

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Data Availability Statement: The data set from the study "Deficits in pain medication in older adults with chronic pain receiving home care: a cross-sectional study in Germany" cannot be shared publicly. According to written informed consent from study participants, information on public deposition of research data was not stated. Data underlying the results in the manuscript are archived in the Institute of Clinical Pharmacology and Toxicology, Charité – Universitätsmedizin Berlin, and can be accessed by all interested researchers on site. Requests should be submitted to reinhold.kreutz@charite.de.

Abstract

Objective

To analyze the pattern and appropriateness of pain medications in older adults receiving home care.

Methods

We performed a prospective cross-sectional study in patients ≥65 years old having chronic pain and receiving home care in Berlin, Germany. Data on prescribed pain medications were collected using self-reported information, nursing documents, and medication plans during interviews at home. Pain intensity was determined with the numeric rating scale (NRS) and the Pain Assessment In Advanced dementia (PAINAD) scale. The Pain Medication Appropriateness Scale score (S_{PMAS}) was applied to evaluate inappropriateness (i.e. a score ≤67) of pain medication.

Results

Overall 322 patients with a mean age of 82.1 ± 7.4 years (71.4% females) were evaluated. The average pain intensity scores during the last 24 hours were 5.3 ± 2.1 and 2.3 ± 2.3 on NRS and PAINAD scale (range 0–10, respectively). Sixty (18.6%) patients did not receive any pain medication. Among the treated patients, dipyrone was the most frequently prescribed analgesic (71.4%), while 50.8% and 19.1% received systemic treatment with opioids and non-steroidal anti-inflammatory drugs, respectively. The observed median S_{PMAS} was 47.6 (range 0–100) with 58 (18.0%) of patients achieving appropriate values. Half of the patients were treated with scheduled, while 29.9% were only treated with on-demand medications. Cognitive status had no effect on appropriateness of pain treatment.

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Competing interests: The authors have declared that no competing interests exist.

Conclusions

We observed substantial deficits in dosing patterns and appropriateness of pain medication in older adults with pain receiving home care. This applied to both patients with and without severe cognitive impairment.

Introduction

The global population has experienced a demographic change over the last century towards an aging population [1]. In Germany, an estimated 3.4 million individuals are in need of care and the majority of them (81%) are more than 65 years old, while 35% are at least 85 years old [2]. For this elderly population, pain represents a significant problem due to the high prevalence of musculoskeletal disorders, cancer, neuropathy and other medical conditions for which pain is a major symptom [3]. The prevalence estimates of chronic pain in the general population in Europe range from 12% to 30%, while in Germany a rate of 17% has been previously reported [4]. A more recent meta-analysis reported that about 62% of the population over the age of 75 years suffered from chronic pain in the UK indicating that the burden of chronic pain increases in line with aging [5]. On the other hand, a previous study indicated that there is an age-dependent discrepancy between the prevalence of chronic pain and pain interference or suffering from chronic pain [6]. Nevertheless, in the elderly it is estimated that about 70% of elderly individuals in home care are suffering from pain [7]. The problem is further complicated in those with cognitive impairment who are mostly incapable of communicating their own symptoms, which hinders appropriate management of pain in this population [8].

While pain itself is not a disease, rather a symptom to a multitude of underlying health disorders, chronic pain is regarded by some as a disease in its own right [9]. The implementation of a separate diagnostic code for chronic pain according to the newest International Classification of Diseases (ICD-11) underlines the need for better care for patients with chronic pain [10].

Uncontrolled pain substantially affects daily activities such as sleeping, housework and social relationships, and despite a plethora of available analgesic drugs, pain remains inadequately treated in most elderly patients [11, 12]. On the other hand, improved pain relief can positively reactivate a person's physical and mental condition [13].

The elderly population is challenging in terms of its complexity and heterogeneity where comorbidity and polypharmacy complicate frailty [14]. Thus, improper use of pain medications and polypharmacy increases the risk of drug interactions and developing adverse drug reactions in the elderly [15]. The latter accounts for a great burden of disease in these patients including the need for hospital admission [16]. Hence, a recent meta-analysis showed that among patients admitted to hospital because of adverse drug reactions, non-steroidal anti-inflammatory drugs (NSAIDs) were frequently related to these admissions (percentages range from 2.3 to 33.3%) [16]. Optimal medical management and nursing care in pain treatment are thus essential to reduce morbidity and costs in long-term care. Nevertheless, to implement appropriate pharmacologic pain management in practice remains a challenging task.

We set out to assess the pattern of prescribed pain medications and their appropriateness in older adults receiving home care. We performed a prospective cross-sectional study in Berlin, Germany, and included patients independently from their cognitive status; thus patients with cognitive impairment were also enrolled.

Methods

Design and setting

The current analysis is a pre-specified analysis of the recently completed *ACHE* study ("Development of a Model for PAin Management in Older Adults ReCeiving Home CarE") in Germany. *ACHE* is an observational cross-sectional study conducted in the home care setting in Berlin, Germany, from May 2017 to April 2019. The study complies with the declaration of Helsinki and was approved by the ethical committee of the Charité, Universitätsmedizin Berlin (EA1/368/14). Written informed consent was obtained by all the patients or their legal guardians in case of cognitive impairment.

Study population

Older adults receiving home care were mainly recruited through ambulatory nursing services (Fig 1) and were included if they met the following criteria: 1) aged 65 years or older; 2) suffering from chronic pain ($\geq$ 3 months); 3) live at their own homes and 4) in need of care according to the legal regulations in Germany. Importantly, patients were enrolled independently from their cognitive status. Thus, we also included patients with cognitive impairment. There were 82 (15%) of 546 ambulatory care stations in Berlin that volunteered to take part in the study. The cognitive state of all patients was assessed using the Mini Mental Status Examination (MMSE) [17].

Data collection

Data were obtained through face-to-face interviews in the patients' own homes by five trained research assistants with different educational and professional qualifications including backgrounds in pharmacy, medical education, social science, nursing, or occupational therapy. Data on pain characteristics, pain management strategies, demographics as well as the level of care were collected and were based primarily on patients' self-report, caregiving relatives, nurses and, if available, medication plans (Table 1). Drug-related data were systematically obtained by scanning medication packages using barcode scanners and the Instrument for Database-assisted Online recording for Medication (IDOM) [18]. The latter is based on detailed classification data provided by the AOK Research Institute (WIdO) that were updated on a monthly basis. All information regarding the active ingredients, the anatomical therapeutic chemical (ATC) classification, dosage, the mode of administration, "over the counter" (OTC)-drugs and nutritional supplements were recorded. Moreover, the investigators asked how patients obtained their drugs (e.g. by prescription, doctor's recommendation or self-medication), the frequency of administration (scheduled or on-demand) as well as the duration of treatment. The gathered information about medications, diagnosis, and pain intensity, as well as pain relief by medications by the physician were utilized later to assess the appropriateness of pain management.

Instruments and measures

Pain management was evaluated by using the Pain Medication Appropriateness Scale (i.e. PMAS) originally designed to detect problems in pain therapy in nursing homes [21]. The PMAS is a valid tool to analyze the pharmacological treatment of pain. To check for scale reliability, Cronbach´s coefficient alpha was calculated for PMAS [22]. This scale consists of ten items allocated to five main domains (appropriate medication for pain syndrome, scheduled dose interval, titration of medication to severity of pain including the pain management index (PMI), constipation prevention, and exclusion of geriatric high-risk drugs). In a previous

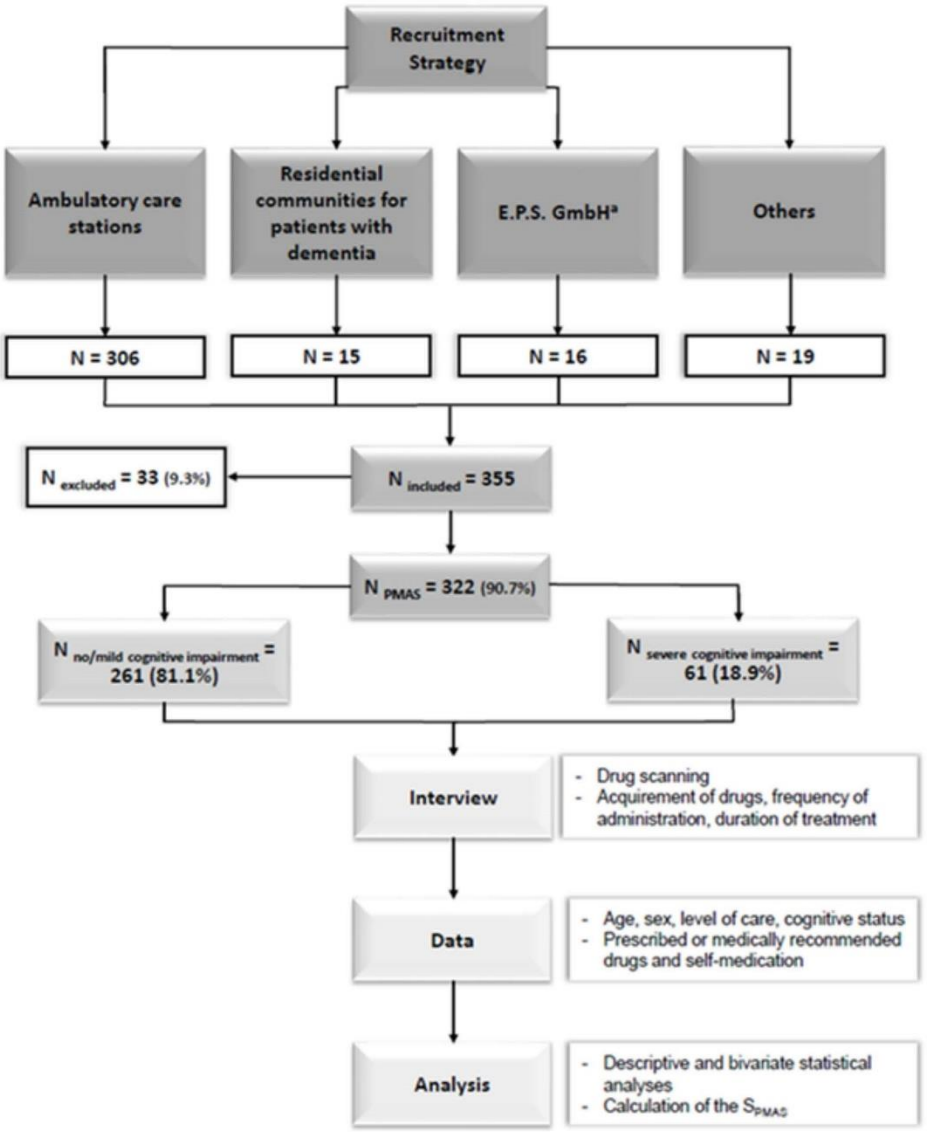

Fig 1. Flowchart—Recruitment strategy and methodical approach. S_{PMAS}, Score on the Pain Medication Appropriateness Scale. [a]E.P.S. GmbH is a service in Germany that provides advices to family caregivers regarding home care related issues.

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Table 1. Patient characteristics.

Characteristics	Full study population			PMAS population		
	Total N = 355	Women N = 254 (71.5%)	Men N = 101 (28.5%)	Total N = 322	Women N = 230 (71.4%)	Men N = 92 (28.6%)
Age (years)	82.2 ± 7.5	83.0 ± 7.1	80.4 ± 8.4	82.1 ± 7.4	82.7 ± 6.9	80.4 ± 8.3
Care level (%)[a]						
1	11.3	9.8	14.8	12.4	10.9	16.3
2	44.8	45.7	42.6	46.6	48.3	42.4
3	21.1	20.1	23.8	20.8	19.6	23.9
4	12.7	13.8	9.9	10.9	11.3	9.8
5	7.3	7.1	7.9	6.8	6.9	6.5
nd	2.8	3.5	1.0	2.5	3.0	1.1
MMSE (%)[b,c]						
0–17 points	22.6	23.7	19.8	18.9	19.5	17.4
18–23 points	15.8	15.4	16.8	15.8	17.0	13.0
24–30 points	61.6	60.9	63.4	65.3	63.5	69.6
Barthel index[d,e]	66.7 ± 27.5	66.9 ± 26.5	66.3 ± 29.9	68.7 ± 26.4	69.4 ± 24.9	67.0 ± 29.8

PMAS, Pain Medication Appropriateness Scale; nd, not determined; MMSE, Mini Mental State Examination.

[a]According to § 15 SGB XI, the level of care is based on the degree of self-dependence and ranges from 1 (lowest degree) to 5 (most severe impairment with special requirements for nursing care).

[b]The MMSE-score was calculated for 354 individuals.

[c]According to the MMSE classification [19]: 0–17 (severe cognitive impairment), 18–23 (mild cognitive impairment), 24–30 (no cognitive impairment).

[d]The Barthel-index was calculated for 349 individuals of the total population and for 319 of the PMAS population.

[e]The motor function restriction is graded by the Barthel index into [20]: 0–15 (very severe), 20–30 (severe), 40–55 (intermediate severe), 60–75 (intermediate), 80–95 (low) and 100 (no or minimal functional impairment).

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study, the PMAS was successfully adapted for the evaluation of pain medication management in Germany [23]. For the evaluation of PMAS, pain intensity was assessed using numeric rating scales (NRS) for pain as implemented within the Brief Pain Inventory (BPI) [24] in patients without cognitive impairment. In patients with an MMSE value <10 or in whom NRS could not be evaluated for other reasons, the Pain Assessment In Advanced Dementia (PAINAD) scale [25] was applied. The corresponding validated German transcript for the PAINAD scale was used [26]. The BPI includes four NRS ranging from 0 (no pain) to 10 (worst imaginable pain) to asses four items of pain intensity (worst pain, lowest pain, average pain, current pain) over the past 24 hours.

The German PAINAD scale consists of five items that focus on characteristic behavior due to pain in patients with advanced dementia as a physical indication of pain suffering (breathing, negative vocalization, facial expression, body language and consolability). For each item considering different behavioral patterns, there is a scale from 0 to 2 and total scores between 0 and 10 are possible.

A checklist for special types of pain was also applied. Functional status was evaluated by the Barthel-Index (BI) [27, 28].

Only medications that were prescribed by the treating physicians were considered for PMAS analysis, including both scheduled and on-demand medications; dosing intervals were also considered. Furthermore, we adapted the PMAS according to current national guidelines of pain management as well as high risk drugs avoided in geriatric patients [29, 30] (S1 Table). In addition, we formulated a four-class categorization of the PAINAD-score using boxplots and substantiated our approach by the Receiving Operating Characteristic (ROC)-curve analysis (S2 Table and S1 Fig) [31].

Each item of the PMAS was assessed if it applied to the patient's individual situation. As a result, there are different maximum points possible. The final PMAS-score (i.e. S_{PMAS}) reflects a percentage considering the possible points ($S_{possible}$), as well as the applicable points (S_{total}) according to the formula [21]:

$$S_{PMAS} = \sum(S_{total}) / \sum(S_{possible}) * 100$$

An $S_{PMAS} \leq 67$ value indicates inappropriate pain medication as suggested [21]. In individuals in whom self-reported pain assessment was not feasible, a score of ≥ 1 on the PAINAD scale indicated probable pain.

Data analysis

Descriptive statistics were used to describe demographics of patients and variables related to pain- and medications. Data were analyzed using IBM SPSS Statistics, version 25 (IBM Corp, Armonk, NY). The analysis of S_{PMAS} is based on an adapted version of the reported German version of the PMAS [23]. The distribution of variables was checked using Shapiro-Wilks test. For data without normal distribution, the non-parametric Mann-Whitney U test or Kruskal-Wallis H test were used as appropriate. Thus, the latter was used to compare S_{PMAS} values of the different subgroups related to the mode of drug intake (only on demand, only scheduled, both, none) and was followed by Dunn-Bonferroni test for posthoc analysis. Data for S_{PMAS} were presented as median and range. Spearman's correlation and Chi-squared test were conducted to check associations between patients'characteristics and the S_{PMAS}. Statistical significance was determined with an alpha value of 0.05.

Results

Study participants

A total of 355 patients (mean age 82.2 ± 7.5 years, 71.5% females) met the formal inclusion criteria of the overall *ACHE* study; data of 322 patients (mean age 82.1 ± 7.4 years, 71.4% females) were available for analysis of appropriateness of pain medication, i.e. PMAS population (Table 1). Patients were excluded because of missing data regarding medication, diagnosis or some other aspects that are necessary to calculate S_{PMAS}. The majority of patients (46.6%) received the second level of care, while for 2.5% the level of care was not determined (Table 1). No or only mild cognitive impairment was observed in 261 (81.1%) patients, while 18.9% had severe cognitive impairment (MMSE ≤17 points). The mean Barthel index was 68.7 ± 26.4. All patients suffered from chronic pain and had an average pain intensity score of 5.3 ± 2.1 on the NRS (range 0–10) during the last 24 hours. The corresponding score was 2.3 ± 2.3 on the PAINAD scale (range 0–10) in patients with cognitive impairment (n = 64). Overall 211 (65.5%) patients reported current pain at the time of interviewing with an average intensity of 5.7 ± 1.9 on the NRS and 3.0 ± 2.2 on the PAINAD scale in the last 24 hours. The mean score for worst pain that was obtained in patients with current pain and without cognitive impairment over the past 24 hours was 6.9 ± 2.1. Almost half of the patients (n = 155) have had chronic pain for at least 10 years. Low back pain (75.8%), osteoarthritis (67.2%) and neuropathic pain (57.1%) were the most frequently recorded underlying pain conditions, besides other diseases such as headache (32.9%), rheumatoid arthritis (14.2%) and urarthritis (12.9%).

Pattern of pain medications

Overall sixty (18.6%) patients did not receive any pain medication and from the 211 patients who reported having current pain during the interview, 37 (17.5%) received no prescribed

pain medication. About half of the patients (162/322) were treated with systemically administered scheduled analgesics. About a quarter of patients (81/322) were only treated with scheduled and 29.9% (96/322) received only on-demand medications.

Dipyrone was most frequently prescribed (Fig 2) in a total of 187 (71.4%) of treated patients of whom 81 (43.3%) patients received dipyrone as monotherapy. The second most frequently prescribed drug was ibuprofen in 38 (14.5%) of treated patients. Only 50 (19.1%) of all treated patients received systemic treatment with any NSAID, either as scheduled or as on-demand medication. Overall 133 (50.8%) patients received treatment with systemic opioids most frequently as scheduled treatment (n = 118), but only 45.8% of the latter were prescribed additional treatment with laxatives for constipation prophylaxis.

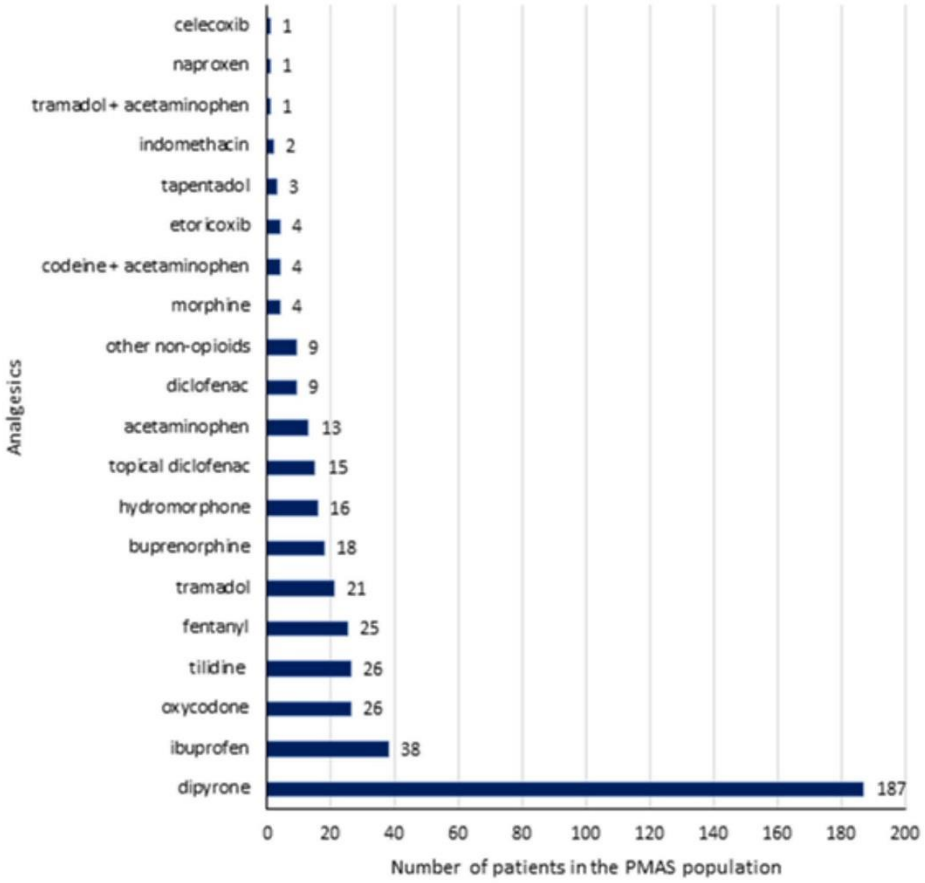

Fig 2. Numbers of individuals with prescribed analgesics among the PMAS population. PMAS, Pain Medication Appropriateness Scale.

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Appropriateness of pain medications

The observed median S_{PMAS} was 47.6 (range 0–100). The PMAS was reliable with a value of 0.83 for Cronbach´s alpha. According to the suggested cutoff of ≤67 [21], only 58/322 (18.0%) of patients received adequate pain medication. S_{PMAS} in patients with prescribed analgesics was significantly higher (median: 53.3 [range 0–100]) than in subjects without any pain medication (median: 6.7 [range 0–66.7], Mann Whitney test, $U = 1100.5$, $p < 0.001$). Patients who received only on-demand pain medication achieved lower S_{PMAS} values compared to patients treated only with scheduled analgesics (median: 33.3 [range 0–100] vs. 50.0 [range 22.2–83.3], Kruskal-Wallis H test, $H = 197.3$, $p < 0.001$). Patients managed by both scheduled and on-demand medication (n = 84) obtained the highest S_{PMAS} (median: 71.4 [44.4–93.3], Kruskal-Wallis H test, $p < 0.001$). Age, sex, cognitive state, school education, professional qualification, functional state, and pain intensity did not significantly affect appropriateness of pain medication.

We observed a moderate correlation between the number of prescribed analgesics and S_{PMAS} ($r = 0.672$; $p < 0.001$). Patients who achieved an S_{PMAS} ≤67 were treated with an average of 1.1 ± 0.8 (range 0–5) analgesic drugs, while patients with an S_{PMAS} >67 received 2.1 ± 0.8 (range 1–4) medications. A total of 134 (51.1%) patients received only one analgesic, the majority of them had an S_{PMAS} ≤67. Nevertheless, there were 10/58 (17.2%) patients who were adequately treated with monotherapy (Fig 3).

Discussion

In the current cross-sectional study, we identified several important deficits in pain medication treatment in older patients receiving home care in Germany. First of all, 18.6% of patients with a history of chronic pain did not receive any pain medication. Secondly, a substantial number of patients were, in contrast with guideline recommendations [32], only treated with either scheduled (25.2%) or on-demand medications (29.9%). This is important against the background of the history of chronic pain and intensity of current pain as observed during the last 24 hours in our cohort of patients. According to the *MOBILIZE Boston* study [33], about 30% of community-living older adults with moderate to severe pain were also inadequately treated, while 50% did not receive any pain medication [33]. The latter finding might be explained by the relative high ratio of patients with very mild to mild pain enrolled in this study [33]. Roy et al. reported in agreement with our current findings, that 16% of institutionalized elderly patients with pain did not receive treatment with analgesics [34]. We also found in a previous study in the nursing home setting in Germany, that 20.6% of residents with chronic pain received no treatment with pain medications [35].

In agreement with previous findings in Germany [23, 35], dipyrone was by far the most frequently prescribed analgesic in the current study. Despite the well-known risk of agranulocytosis associated with dipyrone [36], the use of this drug seems well justified particularly in the vulnerable elderly population, because of its favorable overall risk-benefit profile as compared to NSAIDs [37, 38]. Although ibuprofen was the second most frequently prescribed drug in our study, the overall prescription rate of systemic NSAIDs was relatively low (19.1%). Their use is rated negatively in the evaluation of the appropriateness of pain medication in the PMAS tool when prescribed as scheduled medication for a period longer than four weeks. Furthermore, according to the Fit fOr The Aged (FORTA) List, NSAIDs should be generally avoided in the elderly [30]. However, the use of acetaminophen, that is often preferred in elderly patients due to its better safety profile [39], was also very low (5.0%). The latter could be related to the fact that acetaminophen prescriptions in Germany are only reimbursed by health insurances in patients suffering from severe pain and who are treated with opioids [40].

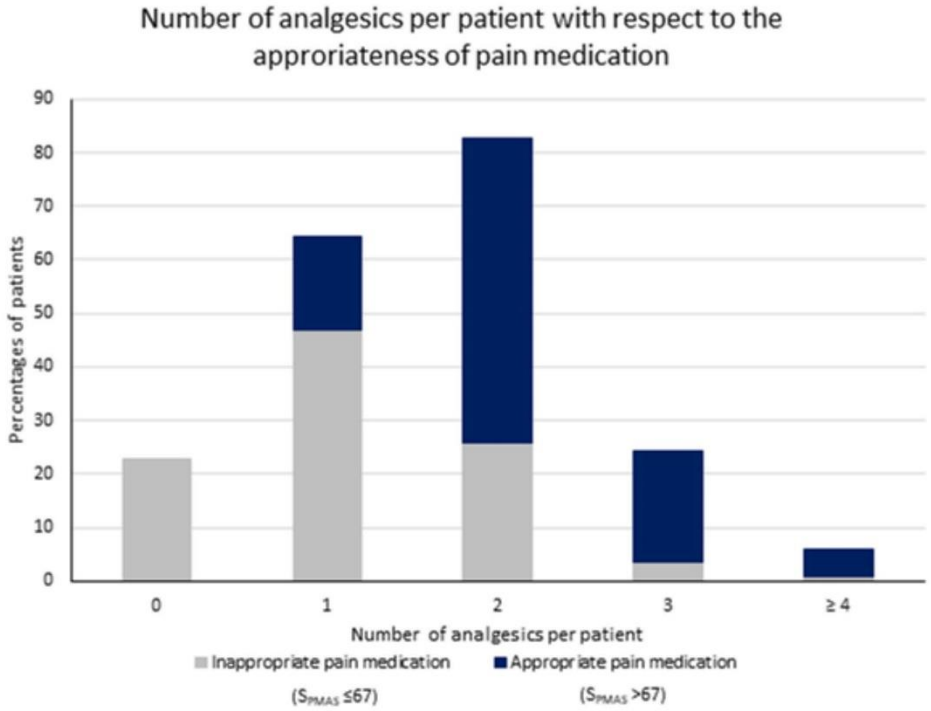

Fig 3. Number of analgesics per patient with respect to the appropriateness of pain medication. S_{PMAS}, Score on the Pain Medication Appropriateness Scale.

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On the other hand, a substantial fraction (50.8%) of treated patients in our study was treated with opioids. This could be ascribed to the observed high prevalence of patients with osteoarthritis, low back pain and neuropathic pain in whom opioids are often recommended [32]. However, the use of opioids for persistent pain is not without limitations particularly in the treatment of older adults because of changes in their pharmacodynamic and pharmacokinetic profile that may require dose adjustments [41]. Their long-term use may result in serious adverse effects such as sedation, impaired balance and falls [41] in the vulnerable elderly population exposed to polypharmacy [42].

When considering appropriateness of pain medication, less than one fifth (18%) of patients received adequate pain treatment according to the suggested S_{PMAS} cutoff value >67 [21]. Our results are thus consistent with a corresponding study in the nursing home setting in Germany that reported also deficits in pain treatment, although with a somewhat higher percentage of patients (i.e. 24%) receiving appropriate treatment [23, 43]. A more recent study by Rabenberg et al. substantiated our results by reporting deficits in pain treatment in the elderly [44]. In their study, one out of ten older patients had a problem (under- or over-treatment) with pain medications [44].

One strength of our study is related to the fact that we included also patients with severe cognitive impairment (18.9%). This is in contrast to previous studies that either included only a very small number of these patients [21] or excluded patients with moderate to severe

cognitive impairment [33] or dementia [45]. In order to assess the appropriateness of pain medication in the patients with severe cognitive impairment, we used a four-class categorization of the PAINAD-score to assess pain severity in this group of patients with a cutoff value of 1 for mild pain (S3 Table). In the literature, a cutoff score of 2 on the PAINAD scale indicates likely pain in patients with dementia, nevertheless, pain cannot be ruled out with a score less than 2 for cognitively impaired individuals [46].

The observed positive correlation between the number of analgesics and S_{PMAS} in the current study is not surprising. A combination of two or more analgesics with complementary mechanisms of action is projected to provide greater pain relief [32]. However, this does not always imply that patients with the highest number of analgesics are treated best. It is equally important to consider the class of drug in relation to the pain condition, the dosage, dosing interval and the mode of application that also affect appropriateness within the evaluation using PMAS. Indeed, there were patients in our sample treated with analgesic monotherapy who reached the threshold for appropriate treatment (S_{PMAS} >67). In addition, the combined prescription of fast-onset, short-acting, on-demand analgesics with scheduled analgesics for breakthrough pain is useful for optimal pain control [32]. This is corroborated by our finding where patients treated with both scheduled and on-demand analgesics reached the highest S_{PMAS}. In analogy to regularly-administered medications, clear information regarding the dose (initial and maintenance), the dosing interval and the duration of treatment should be provided to patients when on-demand medications are prescribed [47].

As a case in point, we noticed that for 40.6% of prescribed on-demand analgesics, the dosing interval was unknown. In these cases, we could not assess whether these analgesics were adequately dosed by physicians. As a result, no additional points for adequate dosing intervals were considered during evaluation.

Our study has some limitations. First, we analyzed only a relatively small sample because access to this study population is very difficult to achieve in Germany. Second, the patients were interviewed/observed only once, i.e. at a single occasion. Third, no interrater reliability validity was done in our study. However, interrater reliabilities in our previous studies using a similar overall approach were found to be satisfactory and highly significant [23, 35]. The PMAS has also some limitations as previously pointed out [21, 23, 35]. Thus, in the calculation of the S_{PMAS}, non-pharmacological pain treatment is not considered. The potential of this treatment modality should not be underestimated, especially in the elderly where side effects of medications, drug-drug interactions, and comorbidities can impede the use of pharmacological treatments [48]. The combination of non-pharmacological and pharmacological pain management is important for effective pain relief [14, 49]. Furthermore, no points are considered for treatment with co-analgesic drugs. Although co-analgesics are in general not primarily indicated to treat pain, they are efficacious when combined with other analgesics [32, 50] and may also be prescribed as monotherapy for special pain syndromes [32]. Nevertheless, the PMAS tool is best known for its reliability and flexibility [43], whereby items could be eliminated during assessment if they do not apply to individual patients. Accordingly, we modified this scale in agreement with current recommendations regarding the use of cannabinoids in the treatment of chronic pain [51, 52]. In addition, a moderate to high level for scale reliability for the PMAS was indicated by a Cronbach´s alpha value of 0.83 [22].

Conclusions and implications

We observed substantial deficits related to lack of treatment, inadequate dosing patterns and overall high frequency of inappropriate use of pain medications in older adults with pain receiving home care. Therefore, interventional strategies to improve treatment by

implementing a multidisciplinary network approach involving physicians, pharmacists, nurses and patients, possibly supported by modern eHealth tools [53] is highly warranted.

Supporting information

S1 Fig. Box plot used for the four-class categorization of the PAINAD-score. In consideration of all patients for whom the PAINAD sum score was available (n = 81), an appropriate four class categorization was not possible (A). For further explorative data analyses, we excluded patients with a total sum score of 0 on the PAINAD-scale (n = 57). Thus, we got a boxplot indicating four classes of the PAINAD sum score (B) as described in S2 Table.
(DOCX)

S1 Table. Modification of the German version of the pain medication appropriateness scale (PMAS). PMAS, Pain Medication Appropriateness Scale; NSAIDs, non-steroidal anti-inflammatory drugs; PRISCUS list, Potentially Inappropriate Medications in the Elderly.
(DOCX)

S2 Table. Four class categorizations of the PAINAD-score.
(DOCX)

S3 Table. The PAINAD-score cutoff according to ROC curve. With regard to the highest level of sensitivity and specificity, a PAINAD score greater than 0.5 was chosen to determine cognitively impaired patients with pain-associated physical expressions. ROC, Receiving Operating Characteristic.
(DOCX)

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Author Contributions

Conceptualization: Andrea Budnick, Dagmar Dräger, Reinhold Kreutz.

Formal analysis: Juliana Schneider, Engi Algharably, Andrea Budnick, Reinhold Kreutz.

Funding acquisition: Andrea Budnick, Dagmar Dräger, Reinhold Kreutz.

Investigation: Juliana Schneider, Arlett Wenzel.

Methodology: Juliana Schneider, Andrea Budnick, Arlett Wenzel, Dagmar Dräger, Reinhold Kreutz.

Project administration: Andrea Budnick, Dagmar Dräger, Reinhold Kreutz.

Supervision: Dagmar Dräger, Reinhold Kreutz.

Visualization: Juliana Schneider, Engi Algharably.

Writing – original draft: Juliana Schneider, Engi Algharably.

Writing – review & editing: Juliana Schneider, Engi Algharably, Andrea Budnick, Arlett Wenzel, Dagmar Dräger, Reinhold Kreutz.

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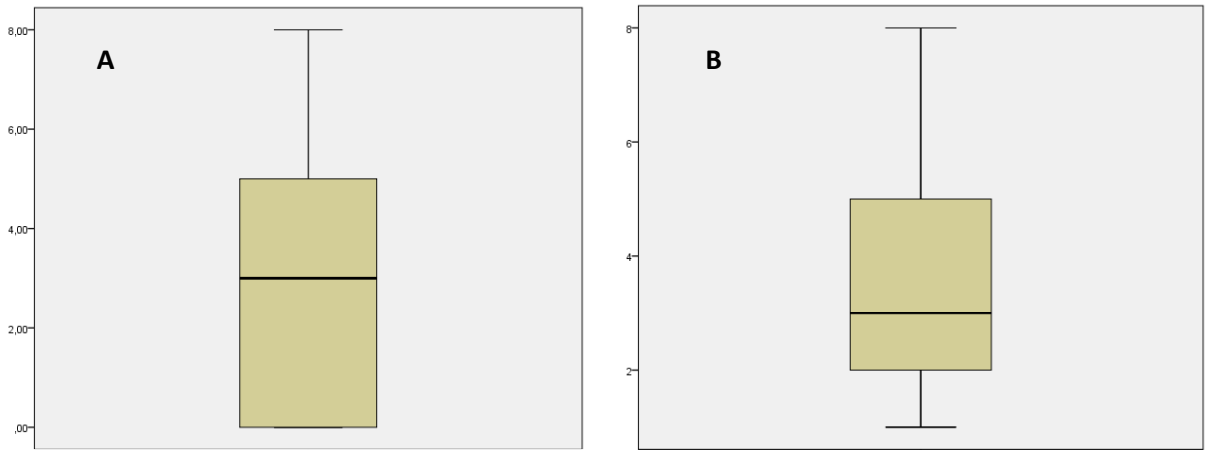
Anhänge zu Publikation 2



S1 Figure. Box plot used for the four-class categorization of the PAINAD-score.

In consideration of all patients for whom the PAINAD sum score was available (n=81), an appropriate four class categorization was not possible (A). For further explorative data analyses, we excluded patients with a total sum score of 0 on the PAINAD-scale (n=57). Thus, we got a boxplot indicating four classes of the PAINAD sum score (B) as described in S2 Table.

S1 Table. Modification of the German version of the Pain Medication Appropriateness Scale (PMAS).

Item on the PMAS	Modification
Item 2. Neuropathic pain:	▪ Points were also possible for capsaicin and cannabinoids.
Item 6. Pain severity – calculation of the Pain Management Index (PMI):	▪ Cannabinoids were considered as non-opioid analgesics and were scored with 1 point. ▪ Tapentadol was considered as a strong opioid and was scored with 3 points.
Item 9. Appropriate constipation prevention with scheduled opioids:	▪ It is possible, to add points to reach 3/3 points.
Item 10. Drugs to avoid in geriatric patients:	▪ - 1 point for routine dosing of NSAIDs excluding topical NSAIDs ▪ - 1 point for antiarrhythmic drugs of class 1 and sotalol ▪ - 1 point for clonidine excluding topical clonidine ▪ - 1 point for H_1-antihistamines according to PRISCUS list ▪ - 1 point for promethazine and strong sedative neuroleptics excluding melperone and pipamperon ▪ - 1 point for anticholinergic muscle relaxants or antispasmodics (orphenadrine, hyoscyamine, atropine, oxybutynin, solifenacin, tolterodine (not retarded), baclofen and tetrazepam)

PMAS, Pain Medication Appropriateness Scale; NSAIDs, non-steroidal anti-inflammatory drugs; PRISCUS list, Potentially Inappropriate Medications in the Elderly.

S2 Table. Four class categorizations of the PAINAD-score.

Categories	Pain severity
0	No observed pain pattern
1 - 2	Mild pain
3 - 4	Moderate pain
≥ 5	Severe pain

S3 Table. The PAINAD-score cutoff according to ROC curve.

Positive, if greater than or equal to a.	Sensitivity	1 - Specificity
-1,00	1,000	1,000
,50	1,000	,400
1,50	1,000	,225
2,50	1,000	,000
3,50	,683	,000
4,50	,561	,000
5,50	,341	,000
6,50	,146	,000
7,50	,098	,000
9,00	,000	,000

a. The smallest cutoff value is the minimum observed rest value minus 1, and the largest cutoff value is the maximum observed test value plus 1. All the other cutoff values are the averages of two consecutive ordered observed test values.

With regard to the highest level of sensitivity and specificity, a PAINAD score greater than 0.5 was chosen to determine cognitively impaired patients with pain-associated physical expressions. ROC, Receiving Operating Characteristic.

6.3 **Publikation 3: Schneider J**, Algharably EAE, Budnick A, Wenzel A, Dräger D, Kreutz R. High prevalence of multimorbidity and polypharmacy in elderly patients with chronic pain receiving home care are associated with multiple medication-related problems. *Frontiers in Pharmacology*. 2021 Jun;12:686990.

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5	Annual Review of Pharmacology and Toxicology	7,812	11.250	0.007970
6	DRUG RESISTANCE UPDATES	3,165	11.000	0.004220
7	PHARMACOLOGY & THERAPEUTICS	16,615	10.557	0.023490
8	MEDICINAL RESEARCH REVIEWS	4,974	9.300	0.005360
9	BRITISH JOURNAL OF PHARMACOLOGY	34,040	7.730	0.031300
10	JOURNAL OF CONTROLLED RELEASE	49,132	7.727	0.051270
11	ALIMENTARY PHARMACOLOGY & THERAPEUTICS	21,233	7.515	0.032840
12	DRUG DISCOVERY TODAY	15,022	7.321	0.020720
13	Acta Pharmaceutica Sinica B	3,560	7.097	0.006580
14	NEUROPSYCHOPHARMACOLOGY	26,281	6.751	0.040680
15	European Heart Journal-Cardiovascular Pharmacotherapy	521	6.696	0.001640
16	CLINICAL PHARMACOLOGY & THERAPEUTICS	16,749	6.565	0.018290
17	DRUGS	11,128	6.189	0.014190

18	Neurotherapeutics	4,998	6.035	0.009520
19	PHARMACOLOGICAL RESEARCH	13,517	5.893	0.019090
20	EXPERT OPINION ON THERAPEUTIC PATENTS	3,350	5.611	0.005090
21	EXPERT OPINION ON THERAPEUTIC TARGETS	5,169	5.473	0.007470
22	JOURNAL OF ANTIMICROBIAL CHEMOTHERAPY	32,470	5.439	0.048840
23	BIODRUGS	1,803	5.313	0.002980
24	International Journal of Nanomedicine	23,279	5.115	0.028200
25	EXPERT OPINION ON INVESTIGATIONAL DRUGS	4,833	5.081	0.006230
26	ACTA PHARMACOLOGICA SINICA	9,668	5.064	0.009310
27	BIOCHEMICAL PHARMACOLOGY	27,929	4.960	0.020770
28	ANTIMICROBIAL AGENTS AND CHEMOTHERAPY	67,707	4.904	0.082760
29	DRUG DELIVERY	5,590	4.902	0.008420
30	Expert Opinion on Drug Discovery	3,427	4.887	0.006290
31	INTERNATIONAL JOURNAL OF PHARMACEUTICS	48,995	4.845	0.034660
32	Expert Opinion on Drug Delivery	6,690	4.838	0.007220
33	CURRENT OPINION IN PHARMACOLOGY	6,720	4.807	0.009270
34	CNS DRUGS	4,768	4.786	0.007670
35	JOURNAL OF FOOD AND DRUG ANALYSIS	3,897	4.727	0.005550
36	Biomedicines	1,156	4.717	0.002850
37	Reviews of Physiology Biochemistry and Pharmacology	805	4.700	0.000670
38	Current Neuropharmacology	4,178	4.668	0.006280
39	INTERNATIONAL JOURNAL OF ANTIMICROBIAL AGENTS	12,403	4.621	0.017890

40	CLINICAL PHARMACOKINETICS	8,919	4.604	0.008920
41	EUROPEAN JOURNAL OF PHARMACEUTICS AND BIOPHARMACEUTICS	16,822	4.604	0.014330
42	BIOMEDICINE & PHARMACOTHERAPY	25,449	4.545	0.041300
43	NEUROPHARMACOLOGY	21,682	4.431	0.033110
44	Pharmaceutics	3,227	4.421	0.004080
45	PROGRESS IN NEURO-PSYCHOPHARMACOLOGY & BIOLOGICAL PSYCHIATRY	11,179	4.361	0.013670
46	PHARMACOPSYCHIATRY	1,787	4.340	0.001580
47	INTERNATIONAL JOURNAL OF NEUROPSYCHOPHARMACOLOGY	6,749	4.333	0.011150
48	MOLECULAR PHARMACEUTICS	18,599	4.321	0.026080
49	Pharmaceuticals	3,357	4.286	0.004710
50	PHYTOMEDICINE	11,272	4.268	0.008460
51	Therapeutic Advances in Chronic Disease	721	4.257	0.001700
52	**Frontiers in Pharmacology**	**18,650**	**4.225**	**0.042330**
53	CURRENT MEDICINAL CHEMISTRY	17,243	4.184	0.012960
54	VASCULAR PHARMACOLOGY	3,141	4.152	0.004980
55	Journal of Neuroimmune Pharmacology	2,809	4.113	0.003520
56	ANTIVIRAL RESEARCH	8,708	4.101	0.014670
57	TOXICOLOGY	13,677	4.099	0.007760
58	PHYTOTHERAPY RESEARCH	14,260	4.087	0.008800
59	CNS Neuroscience & Therapeutics	3,598	4.074	0.005870
60	CARDIOVASCULAR DRUGS AND THERAPY	2,114	4.069	0.003340

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ORIGINAL RESEARCH
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High Prevalence of Multimorbidity and Polypharmacy in Elderly Patients With Chronic Pain Receiving Home Care are Associated With Multiple Medication-Related Problems

Juliana Schneider[1], *Engi Abd Elhady Algharably*[1], *Andrea Budnick*[2], *Arlett Wenzel*[2], *Dagmar Dräger*[2] *and Reinhold Kreutz*[1]*

[1]Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Institute of Clinical Pharmacology and Toxicology, Berlin, Germany, [2]Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Institute of Medical Sociology and Rehabilitation Sciences, Berlin, Germany

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***Correspondence:**
Reinhold Kreutz
reinhold.kreutz@charite.de

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Aim: To measure the extent of polypharmacy, multimorbidity and potential medication-related problems in elderly patients with chronic pain receiving home care.

Methods: Data of 355 patients aged ≥65 years affected by chronic pain in home care who were enrolled in the *ACHE* study in Berlin, Germany, were analyzed. History of chronic diseases, diagnoses, medications including self-medication were collected for all patients. Multimorbidity was defined as the presence of ≥2 chronic conditions and levels were classified by the Charlson-Comorbidity-Index. Polypharmacy was defined as the concomitant intake of ≥5 medications. Potentially clinically relevant drug interactions were identified and evaluated; underuse of potentially useful medications as well as overprescription were also assessed.

Results: More than half of the patients (55.4%) had moderate to severe comorbidity levels. The median number of prescribed drugs was 9 (range 0–25) and polypharmacy was detected in 89.5% of the patients. Almost half of them (49.3%) were affected by excessive polypharmacy (≥10 prescribed drugs). Polypharmacy and excessive polypharmacy occurred at all levels of comorbidity. We detected 184 potentially relevant drug interactions in 120/353 (34.0%) patients and rated 57 (31.0%) of them as severe. Underprescription of oral anticoagulants was detected in 32.3% of patients with atrial fibrillation whereas potential overprescription of loop diuretics was observed in 15.5% of patients.

Conclusion: Multimorbidity and polypharmacy are highly prevalent in elderly outpatients with chronic pain receiving home care. Medication-related problems that could impair safety of drug treatment in this population are resulting from potentially relevant drug interactions, overprescribing as well as underuse.

Keywords: chronic pain, comorbidity, drug-drug interactions, elderly, medication-related problems, multimorbidity, outpatient, polypharmacy

INTRODUCTION

Over the last few decades, the population of older adult has grown worldwide especially in the developed countries (Mathers et al., 2015). Between 2000 and 2016, the global life expectancy increased by 5.5 years with a mean age of 72 years (World Health Organization, 2019). The number of individuals having two or more chronic conditions, referred to as multimorbidity has also increased with population aging according to a WHO World Health Survey reporting data from 28 countries between 2001 and 2004 (Afshar et al., 2015). The average number of chronic diseases per patient aged over 60 years was estimated to be 5.3 in men and 5.7 in women in Germany (Kostev and Jacob, 2018). Multimorbidity is associated with poorer health outcomes (Xu et al., 2017), higher mortality rates (McPhail, 2016) and impacts profoundly on healthcare utilization and costs (McPhail, 2016).

Polypharmacy is a common clinical consequence of multimorbidity in older adults encompassing not only prescribed but also over-the-counter medications including among others herbal supplements (Pitkälä et al., 2016). Commonly defined as the concomitant use of ≥5 medications daily (Masnoon et al., 2017), polypharmacy is a formidable problem posing a multitude of negative health outcomes (Maher et al., 2014). It increases the risk of adverse drug reactions, adverse drug events (e.g., falls, fractures, and acute kidney injury), inappropriate medication, medication errors, drug-drug interactions (DDI) and increased risk of mortality (Maher et al., 2014; Chang et al., 2020). Moreover, polypharmacy reduces adherence to appropriate pharmacotherapy and may contribute to physical disability and lower cognitive functions (Wastesson et al., 2018). Optimizing prescribing for elderly is of paramount importance as it can improve health outcomes in multimorbid vulnerable patients e.g., patients with chronic pain. Those patients are particularly susceptible to high multimorbidity burdens as well as risk of polypharmacy (Hubbard et al., 2015; Nakad et al., 2020). Moreover, a strong association was found between a high burden of comorbidity and pain severity in elderly (Leong et al., 2007; Blyth et al., 2008). We therefore aimed to analyze the extent of multimorbidity and polypharmacy in elderly chronic pain patients receiving home care and assessed potential medication-related problems in this target group.

MATERIAL AND METHODS

Design and Setting

The current analysis is a planned pre-specified subanalysis of the *ACHE* study ("Development of a Model for PAin Management in Older Adults ReCeiving Home CarE") in Germany. Briefly, *ACHE* was an observational cross-sectional analysis of a population-based cohort of older adults which focused on pain management in home care and has been described previously in detail (Schneider et al., 2020). Ethical approval was obtained by the local ethical committee of the Charité, Universitätsmedizin Berlin (EA1/368/14). Written informed consent was obtained from all participants or their legal guardians in case of cognitive impairment.

Study Population

Home-dwelling elderly with chronic pain recruited between 09/2017 and 10/2018 in the framework of *ACHE*, aged ≥65 years receiving home care in the city of Berlin, Germany, were eligible for the study (n = 355). As cognitively impaired older adults are also at increased risk of multimorbidity and the negative consequences of polypharmacy, patients with cognitive impairment were also eligible for inclusion in *ACHE*. Hence, patients were enrolled independently from their cognitive status as determined by the Mini Mental Status Examination (MMSE) (Tombaugh and McIntyre, 1992).

Data Collection

Five trained investigators interviewed the participants, collected demographic data, the level of care as well as the education level (highest school education and highest professional education) and documented the concurrent medications used regularly or as needed based on drug packages and medication plans available at participants' homes. According to the Pharmaceutical Care Network Europe (PCNE) classification (Griese-Mammen et al., 2018), we performed an intermediate medication review (PCNE type 2A) based on medication history and patient information. Medications were documented by means of the Instrument for Database-assisted Online recording for Medication (IDOM) (Mühlberger et al., 2003) that based on the data provided by the AOK Research Institute (WIdO). In total, 91 (2.5%) drugs were excluded from medication analysis according to our pre-specified criteria (**Figure 1**).

For the assessment of comorbidities, history of chronic diseases was obtained by thoroughly reviewing the participants' medical records, physician reports, nursing records as well as self-reported diagnoses. Polypharmacy was defined as the concomitant intake of ≥5 medications whereas excessive polypharmacy as ≥10 medications, taken regularly or on-demand (Wastesson et al., 2018). Our analysis encompassed all medications including nutraceuticals prescribed by physician(s) or used in self-medication and focused on pharmacologically active ingredients. Drugs were categorized according to the Anatomical Therapeutic Chemical (ATC) classification system. We checked for relevant DDI, over- and underprescriptions in the concurrently prescribed medications within the general context of medication errors defined as events happening during drug treatment and could cause harm to the patient [Pharmacovigilance Risk Assessment Committee (PRAC), 2015]. Regarding the prescription frequency of drug classes and their relevance to our target group, clinically relevant DDI were checked for anticoagulants, diuretics, and statins, namely simvastatin, using our available institutional drug information system AiDKlinik® and their severity was rated on a case-by-case basis by three clinical pharmacologists/pharmacists (JS, EA, RK) according to our pre-defined criteria. In our evaluation of DDI, we also took into account the vulnerable nature of elderly patients and their susceptibility to more risk and more harmful consequences of DDI than that expected in younger patients.

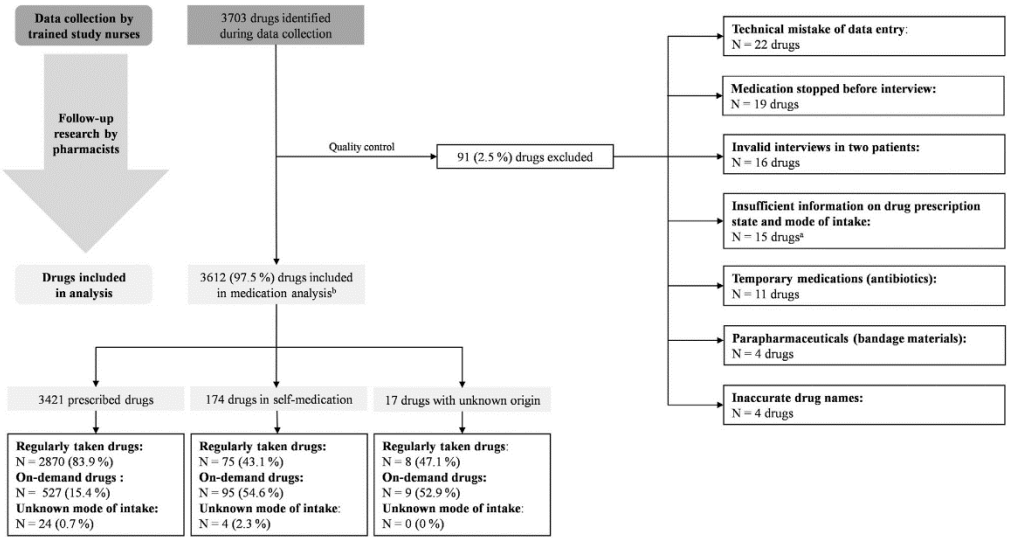

FIGURE 1 | Flow-diagram showing medication screening and selection process. [a]All drugs were non-prescription drugs. [b]Different patients may use the same drug.

Instruments and Measures

The individuals' burden of current diseases in chronic pain patients was assessed by the original Charlson-Comorbidity-Index (CCI) (Charlson et al., 1994) which is a widely used multimorbidity score in older adults (Diederichs et al., 2011). It represents a weighted index of comorbidity based on 19 chronic diseases according to International Classification of Diseases (ICD) diagnosis codes that are weighted differently according to the relative mortality risk (Charlson et al., 1987). We adapted the CCI for use in our population to include also self-reported diagnoses terms when physician reports or nursing records were unavailable. Furthermore, we checked for other chronic diseases such as hypertension, coronary artery disease and atrial fibrillation (AF) besides those listed in the CCI. Multimorbidity was defined as the presence of ≥2 chronic conditions (Kostev and Jacob, 2018). Levels of comorbidity were classified according to the original CCI score as: 0 (no comorbidity), 1–2 (low comorbidity), 3–4 (moderate comorbidity) and ≥5 (severe comorbidity) (Charlson et al., 1987).

We used the CHA_2DS_2-VASc [Congestive heart failure/left ventricular dysfunction, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled) – Vascular disease, Age 65–74, and Sex category (female)] score for patients with AF to evaluate their risk of thromboembolism (Hindricks et al., 2021).

Data Analysis

Descriptive statistics were used to describe patients' demographics, multimorbidity and medications. Variables were checked for normal distribution by Shapiro-Wilk test and non-parametric tests were used according to the type of variable (continuous or categorical). We used Mann-Whitney U test to check the association of the CCI score (continuous) with sex (categorical), prevalence of polypharmacy (categorical) and excessive polypharmacy (categorical). Chi-squared test was used to examine the association between sex and both polypharmacy and excessive polypharmacy as well as the association of comorbidity levels (categorical) with level of care (categorical) and education level [highest school education (categorical) and highest professional education (categorical)]. Spearman's correlation was used to test the correlation between the CCI score and the number of prescribed medications (continuous), age (continuous) and MMSE score (continuous). Kruskal-Wallis H test was used for associations between number of prescribed medications (continuous) and levels of comorbidity (categorical with >2 groups). The post-hoc Dunn-Bonferroni test was applied for pairwise comparison between the groups. In addition, we used the Jonckheere-Terpstra test to check for an overall trend between the groups and calculated the corresponding Kendall's tau-b (τ) correlation coefficient. Data were analyzed using IBM SPSS Statistics, version 25 (IBM Corp, Armonk, NY). Two-tailed statistical significance was assessed at level 0.05.

RESULTS

Study Population

A total of 355 patients met the formal inclusion criteria of the *ACHE* study and data were analyzed as two cohorts: the medication-analysis cohort and the multimorbidity cohort

TABLE 1 | Patients' characteristics.

Characteristics	Population for medication analysis			Population for multimorbidity analysis		
	Total *N* = 353 (99.4%)	Women *N* = 253 (71.7%)	Men *N* = 100 (28.3%)	Total *N* = 334 (94.1%)	Women *N* = 239 (71.6%)	Men *N* = 95 (28.4%)
Age (years)	82.2 ± 7.5	83.0 ± 7.1	80.2 ± 8.3	82.2 ± 7.6	82.8 ± 7.1	80.4 ± 8.5
Care level (%)[a]						
1	11.3	9.9	15.0	11.7	10.5	14.7
2	44.8	45.4	43.0	46.1	46.9	44.2
3	21.0	20.2	23.0	21.2	20.1	24.2
4	12.7	13.8	10.0	11.4	12.5	8.4
5	7.4	7.1	8.0	6.9	6.7	7.4
nd	2.8	3.6	1.0	2.7	3.3	1.1
MMSE (%)[b,c]						
0–17 points	22.7	23.8	20.0	19.1	20.5	15.8
18–23 points	15.7	15.5	16.0	16.2	15.5	17.9
24–30 points	61.6	60.7	64.0	64.7	64.0	66.3
Number of all drugs[d] [median, (range)]	10 [0–25]	10 [0–22]	10 [2–25]	10 [0–25]	10 [0–22]	10.5 [2–25]
Number of prescribed drugs[d] [median, (range)]	9 [0–25]	9 [0–22]	10 [2–25]	10 [0–25]	10 [0–22]	10 [2–25]
Polypharmacy (%)[d] (≥ 5 prescribed drugs)	89.5	89.7	89.0	89.2	89.5	88.3
Excessive polypharmacy (%)[d] (≥ 10 prescribed drugs)	49.3	48.2	52.0	51.4	50.2	54.3

nd, not determined; MMSE, Mini Mental State Examination.

[a]*According to § 15 SGB XI, the level of care is based on the degree of self-dependence and ranges from 1 (lowest degree) to 5 (most severe impairment with special requirements for nursing care).*

[b]*The MMSE-score was calculated for 352/353 of the medication population.*

[c]*According to the MMSE classification (Tombaugh and McIntyre, 1992): 0–17 points (severe cognitive impairment), 18–23 points (mild cognitive impairment), 24–30 points (no cognitive impairment).*

[d]*Medication data for 333/334 of the multimorbidity population were available.*

(**Table 1**). For the medication-analysis cohort, data for 353 (99.4%) patients (mean age 82.2 ± 7.5 years, 71.7% females) were available including 22.7% of patients with severe cognitive impairment (MMSE ≤17 points). For the multimorbidity cohort, data of 334 (94.1%) patients (82.2 ± 7.6 years, 71.6% females) were available and 19.1% of them had severe cognitive impairment.

The most common diseases found in the multimorbidity cohort were hypertension (78.4%), congestive heart failure (CHF) (41.3%), diabetes with/without organ damage (32.1%), dementia (27.2%), coronary heart diseases (26.9%) and chronic pulmonary diseases (25.1%) (**Table 2**). Overall, CCI ranged from 0 to 13 with a median score of 3 (IQR: 2–4) in both men and women with more than half of the patients (55.4%) having moderate to severe comorbidity levels (**Figure 2**). Sex, age, cognitive state, level of care, education level did not significantly affect comorbidity scores. The prevalence of multimorbidity (≥2 chronic diseases) according to the original CCI was 73.7%, and 91.6% when additional disorders detected in the population were counted (**Table 2**).

Medication State

Among the medication-analysis cohort, 3,703 medication products were screened during data collection yielding 3,612 (97.5%) medication products for analysis after screening for data quality as per our preset criteria (**Figure 1**). Of those, 3,421 (94.7%) medication products were prescribed by physicians and 174 (4.8%) were used in self-medication, while for 17 (0.5%) medication products, the prescription mode could not be verified. According to the ATC code, analgesics, diuretics, antithrombotics, renin-angiotensin system (RAS) blockers were most frequently prescribed [**Supplementary Table S1** of the Electronic Supplementary Material (ESM)]. The median number of prescribed drugs was 9 (range 0–25), and 10 (range 0–25) when self-medication was accounted for (**Table 1**). A highly significant positive correlation was found between the CCI and the number of prescribed drugs ($r_s = 0.345$, $p < 0.001$). The prevalence of polypharmacy (≥5 prescribed drugs) was 89.5% ($n = 316$) and almost half of the patients ($n = 174$; 49.3%) were affected by excessive polypharmacy (≥10 prescribed drugs) (**Figure 3**). There were no sex-specific differences for the prevalence of either polypharmacy or excessive polypharmacy (Chi-squared test, $p = 0.842$, and $p = 0.522$, respectively). Patients affected by prescribed polypharmacy had significantly higher CCI scores (median: 3, range 0–13) than patients without polypharmacy (median: 2, range 0–5, Mann Whitney test, $U = 3077.5$, $p < 0.001$). Similarly, excessive polypharmacy was also associated with higher CCI scores (median: 4, range 0–13, Mann-Whitney test, $U = 9271.5$, $p < 0.001$). Moreover, significant associations were found between the number of prescribed medications and different levels of comorbidity (Kruskal-Wallis test, $H = 36.3$, $p < 0.001$). The adjusted p-values of the post-hoc analysis are shown in **Figure 4**. In addition, we found an overall

TABLE 2 | Prevalence of comorbidities among elderly receiving home care (*N* = 334).

Comorbid condition	Assigned weights for comorbidities in the CCI	Patients with comorbidity, N (%)[a]
Comorbidities covered by the CCI		
Congestive heart failure	1	138 (41.3)
Dementia	1	91 (27.2)
Chronic pulmonary disease	1	84 (25.1)
Peripheral vascular disease	1	78 (23.4)
Diabetes[b] with organ damage	2	77 (23.1)
Cerebrovascular disease	1	74 (22.2)
Connective tissue disease	1	50 (15.0)
Myocardial infarction	1	43 (12.9)
Ulcer disease	1	43 (12.9)
Any tumor	2	44 (13.2)
Moderate or severe renal disease	2	39 (11.7)
Diabetes[b] without organ damage	1	30 (9.0)
Mild liver disease	1	27 (8.1)
Hemiplegia	2	16 (4.8)
Metastatic solid tumor	6	6 (1.8)
Moderate or severe liver disease	3	3 (0.9)
Leukemia	2	2 (0.6)
Lymphoma	2	1 (0.3)
AIDS	6	0 (0)
Additional comorbidities detected in *ACHE*		
Hypertension	–	262 (78.4)
Coronary heart disease	–	90 (26.9)
Atrial fibrillation	–	65 (19.5)
Hemiparesis	–	62 (18.6)
Other arrhythmias	–	49 (14.7)
Prostate disorders	–	35 (10.5)

CCI, Charlson Comorbidity Index.
[a]Patients may have more than one comorbidity.
[b]Diabetes includes all patients treated with insulin or oral hypoglycemics, but not diet alone.

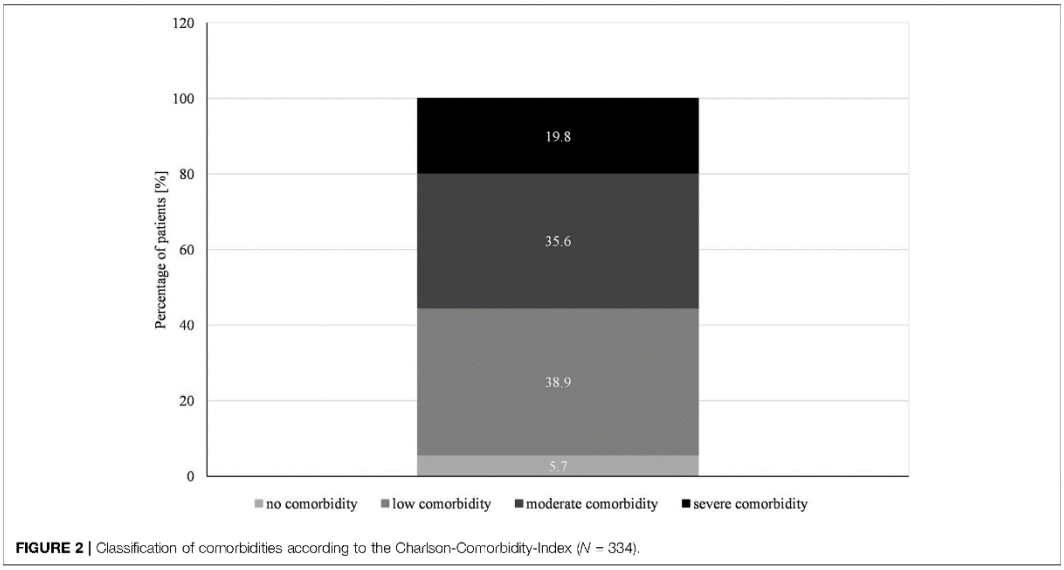

FIGURE 2 | Classification of comorbidities according to the Charlson-Comorbidity-Index (*N* = 334).

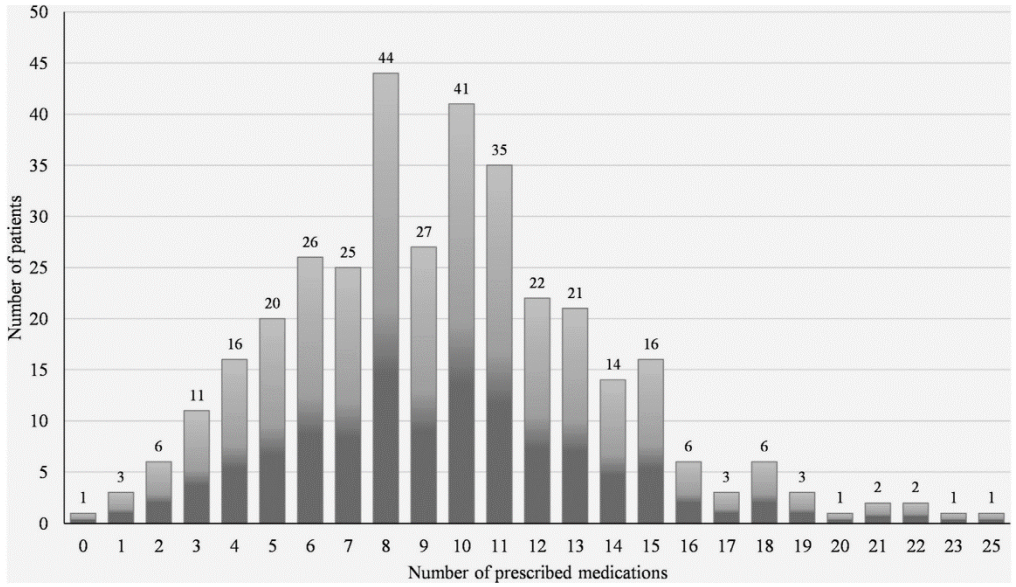

FIGURE 3 | Number of prescribed medications among elderly receiving home care ($N = 353$).

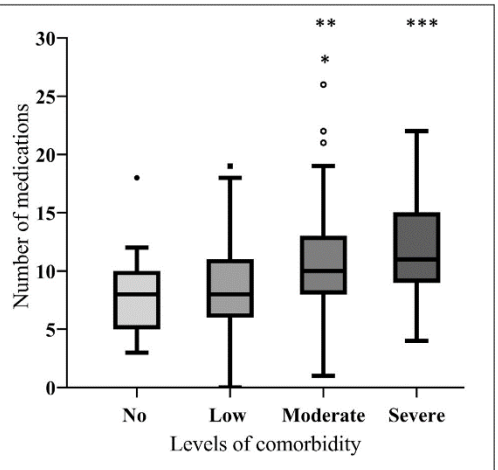

FIGURE 4 | Boxplot diagram: Number of prescribed drugs grouped by different comorbidity levels.*$p < 0.05$ vs. no comorbidity; **$p < 0.01$ vs. low comorbidity; ***$p < 0.001$ vs. low comorbidity; ***$p < 0.001$ vs. no comorbidity.

positive trend between these groups ($\tau = 0.262$, $p < 0.001$). Polypharmacy and excessive polypharmacy were detected in all levels of comorbidity.

Medication Errors Detected in Selected Drugs/Drug Classes (Anticoagulants, Diuretics, and Simvastatin)

In total, 184 clinically relevant potential DDI from which 57 (31.0%) evaluated as severe were detected in more than a third (34.0%) of patients in the medication-analysis cohort (**Supplementary Table S2** of the ESM). DDI lacking clear clinical meaning or consequences were not presented. Over- and underprescription of drugs were detected.

Anticoagulants

Drug-Drug Interactions

A total of 80 patients received anticoagulants in the medication analysis cohort for which 27 potential and 12 severe interactions were detected in 28 (35.0%) patients (**Supplementary Table S2** of the ESM).

Underprescription (Subgroup Analysis for AF)

In our multimorbidity cohort, 65/334 (19.5%) patients (mean age 82.8 ± 7.4 years) had AF (**Table 2**). All of them achieved a CHA_2DS_2-VAS score ≥2 (median: 5; range 3–8) but only 44 (67.7%) patients were anticoagulated with direct oral anticoagulants (DOAC) or vitamin-K-antagonist (VKA), while 21 (32.3%) received no oral anticoagulants; of these, 19 patients were ≥75 years old. The three most prescribed anticoagulants were apixaban (36.4%), phenprocoumon (29.5%) and rivaroxaban (20.5%).

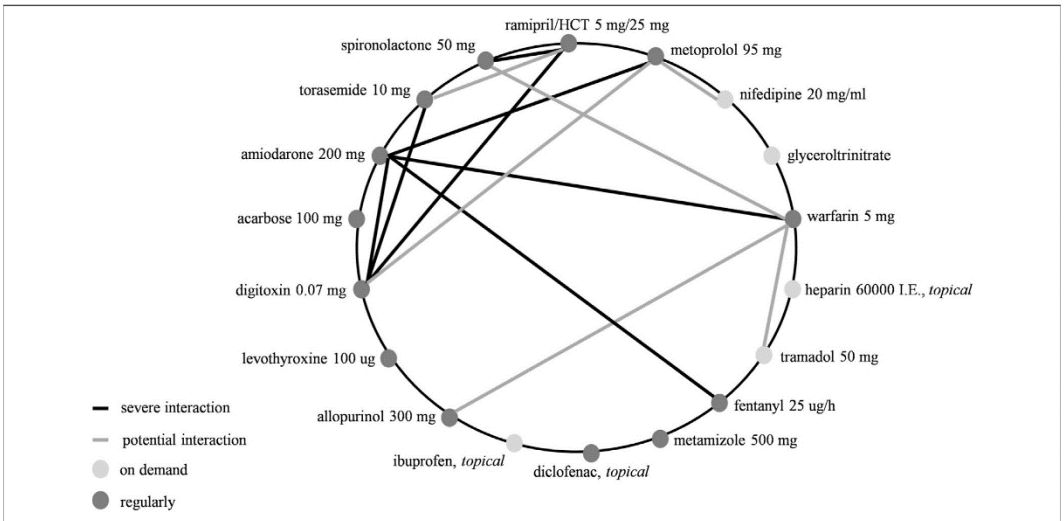

FIGURE 5 | Drug-drug interactions of prescribed medication in one patient.

Diuretics

Drug-Drug Interactions

Among the diuretics, all diuretic agents including potassium-sparing diuretics were included in DDI evaluation amounting to 281 diuretic prescriptions in 224 patients. We found 131 potential DDI, 36 (27.5%) of them were evaluated as severe (**Supplementary Table S2** of the ESM).

Overprescription (Subgroup Analysis for Loop Diuretics)

A total of 195/334 (59.9%) patients were treated with diuretics. By far, the most commonly prescribed diuretic was torasemide, prescribed in 160 (82.1%) patients. Loop diuretics were combined with thiazide/thiazide-like diuretics in 11/195 (5.6%) patients. In one patient, torasemide and furosemide were even co-prescribed. Among 174 (89.2%) patients receiving loop diuretics, 27 (15.5%) patients had no documented indication for CHF, advanced chronic kidney disease or edema.

Simvastatin

Overall, 85/353 (24.1%) patients took simvastatin once daily in an average dose of 29.9 ± 14.5 mg. We found 17 potential DDI between simvastatin and other drugs (e.g., amlodipine, dronedarone, colchicine, ranolazine). Of these, 11 interactions were rated as severe (**Supplementary Table S2** of the ESM).

Demonstration of Patient Case Study Affected by Excessive Polypharmacy and DDI

One patient (83 years, female) for whom we checked the whole DDI profile appears of interest (**Figure 5**). The patient had following comorbidities: hypertension, CHF, AF, diabetes with organ damage, connective tissue disease, edema, and hemiparesis. She was prescribed 18 different drugs by the physician. The patient had suffered a stroke in the past, had a CHA_2DS_2-VASc score of 8 and a CCI score of 5. We identified 13 potential clinically relevant interactions. Of these, seven could be severe (**Supplementary Table S2** and **Figure 5**).

DISCUSSION

The present study revealed that multimorbidity and polypharmacy along with the consequences of polypharmacy (e.g., higher risk of medication errors, DDI, inappropriate medication use) were highly prevalent in our cohort of older adults with chronic pain receiving home care that also included patients with severe cognitive impairment. To the best of our knowledge, this is the first cross-sectional prospective study in Germany to examine the burden of multimorbidity and polypharmacy in this setting involving chronic pain patients. Chronic pain has been reported to be associated with high burden of comorbid diseases and high risk of polypharmacy (Fishbain, 2005; Paladini et al., 2015; Jokanovic et al., 2016). In one study, chronic pain was independently associated with higher daily drug consumption (Ersoy and Engin, 2018).

We found a median CCI score of 3 (IQR: 2–4) in both men and women and an overall range of 0–13. More than half of the patients (55.4%) had moderate (35.6%) to severe (19.8%) comorbidity levels (**Figure 2**). However, these values could be still underestimated considering patients for whom morbidity scores could not be determined due to lack of self-report or medical records. In addition, all patients, by virtue of our study design, had chronic pain. CCI scores ≥3 have been correlated with an increased risk of hospital readmission (Halfon et al., 2002),

while scores ≥5 correlated significantly with mortality and high risk of medication errors (Charlson et al., 1987; Rabenberg et al., 2019). The KORA-Age study (mean age 73.4 ± 6.1 years) reported a median number of conditions of 2 (IQR: 1–3) and a multimorbidity (≥2 chronic conditions) prevalence of 58.6% (95% CI: 57.0-60.2) (Kirchberger et al., 2012). Our higher multimorbidity rate (91.6%) could be ascribed to the home care setting and the older age of our patients. For the assessment of comorbidities, Kirchberger et al. (Kirchberger et al., 2012) also used a CCI generated self-reported diagnoses and included hypertension, eye diseases, mental and neurological diseases, that were deemed highly relevant for exploring multimorbidity in the elderly (Kirchberger et al., 2012). Bravo and colleagues also extended the Charlson list of 19 comorbidities to include 10 other disorders being significant to mortality or functional decline in long-term care setting such as valvular heart diseases (Bravo et al., 2002). Despite the limitation of the CCI to detect other relevant disorders, the CCI is still widely used to investigate comorbidity in geriatric patients in healthcare research (Jorgensen et al., 2012; Abizanda et al., 2014; Rochon et al., 2014; Gellert et al., 2019).

The median number of prescribed drugs was 9 (range 0–25) and 10 (range 0–25) when self-medication was included. In nursing homes in Germany, an average of 5.9 ± 3 (range 0–16) drugs prescribed concomitantly per resident was reported (Kolzsch et al., 2012), while in general practice, a mean of 4.2 ± 2.7 in men and women aged ≥60 years, about 37% of whom were affected by polypharmacy (≥5 prescribed drugs) (Kostev and Jacob, 2018). We found a higher prevalence of polypharmacy (89.5%) with almost half of the patients (49.3%) having excessive polypharmacy (≥10 prescribed drugs) in our study, which may relate to the high multimorbidity prevalence in our study as a driver for polypharmacy. The mean number of prescribed medications was significantly associated with higher CCI-based morbidity levels supporting the reciprocal link between multimorbidity and polypharmacy. The latter acts as a driver for medication-related morbidity and increases the chance of DDI to which elderly patients are more vulnerable. In our target group, potential DDI were detected in a third of patients.

DDI involving simvastatin, a well-known substrate of cytochrome P450 (CYP) 3A4 (Tiwari et al., 2006) predisposing to myotoxicity were detected. The risk of myotoxicity is elevated with older age as muscle mass decreases (Kellick et al., 2014), with renal impairment, and high dose therapy (Tiwari et al., 2006).

As a case study, we demonstrated the overall DDI profile of a multimorbid female patient affected by excessive polypharmacy and experiencing a complex drug regimen. For this patient, we detected several DDI involving anticoagulants and diuretics. This case also illustrates an increased number of prescribed drugs proportional to a high CCI, with a comorbidity score of 5. Notably, guideline-based treatments for several diseases facilitate polypharmacy as illustrated in this patient treated for CHF, hypertension and AF and was therefore included in the AF subgroup analysis.

Patients with AF and a CHA_2DS_2-VASc score ≥2 should be anticoagulated with DOAC or VKA due to risk of stroke (Hindricks et al., 2021). In our study, 19.5% of patients had AF with a median CHA_2DS_2-VASc score of 5 (range 3–8). However, about a third (32.3%) of them did not receive anticoagulant therapy with either DOAC or VKA suggesting a state of underprescription of potentially useful medications. Though current AF management guidelines recommend oral anticoagulant treatment at age ≥75 years regardless of additional risk factors for stroke (Hindricks et al., 2021), underuse of oral anticoagulant treatment in the elderly with AF has been previously reported (Zarraga and Kron, 2013; Steinberg et al., 2015; Kreutz et al., 2018).

Diuretics, commonly prescribed in the elderly, often cause hypovolemia and hyponatremia which increase the risk of falling that was associated with higher morbidity and mortality in older adults (Maher et al., 2014). Elderly hypertensive patients were more likely to develop hyponatremia after age 75 years (Diaconu et al., 2014). Loop diuretics were prescribed in 15.5% of patients without a documented appropriate indication. This includes edematous disorders due to CHF, hepatic cirrhosis or nephrotic syndrome, and advanced renal insufficiency (Sarafidis et al., 2010). Additionally, 5.6% of patients on diuretics received concomitantly loop diuretics and thiazide/thiazide-like diuretics. Overprescription of loop diuretics without appropriate indication has been reported in 27.5% of nursing home residents (Kölzsch et al., 2010). The concomitant use of spironolactone and ramipril as illustrated in our patient case increases the risk of hyperkalemia; a potentially severe DDI to which the elderly are more sensitive due to potassium homeostasis abnormalities, disorders e.g., diabetes mellitus or use of drugs e.g., RAS blockers and potassium-sparing diuretics (Hunter and Bailey, 2019).

Suboptimal prescribing in elderly includes, besides unnecessary prescribing or overprescribing, underuse or underprescribing of indicated medications (Devik et al., 2018). The latter is defined as failure to prescribe a potentially useful drug and has become a frequent problem leading to adverse clinical consequences e.g., stroke in high risk patients undertreated for atrial fibrillation (Kuijpers et al., 2008). Polypharmacy can also be a driver for medication underuse reported to occur in over 40% of patients with polypharmacy (Kuijpers et al., 2008).

This study is the first to examine the burden of multimorbidity and polypharmacy in older adults with chronic pain receiving home care. The strengths of our study lie in the rigorous evaluation of the drug profile including self-medication and drugs prescribed regularly or on-demand as well as including patients with severe cognitive impairment. In contrast to previous studies that excluded patients with cognitive impairment (Markotic et al., 2013; Nawai et al., 2017), patients with cognitive impairment were eligible for inclusion in *ACHE*. However, the following limitations are acknowledged:

First, this is a cross-sectional cohort study. As such, patients were interviewed once; follow-up data of patients were not available. In addition, contacts with the treating physician were not implemented in the study design. Hence, it was not possible to assess the persistence of polypharmacy or notify the physician in case of suspected DDI or trace the outcome of the potential DDI whether a corrective action was taken by the physician or a follow-up for clinical condition was undertaken. Second, our sample size

was small, and the study reflects local data to the city of Berlin regarding patients with chronic pain in the home care setting which may limit the generalizability of our findings concerning prevalence rates of multimorbidity and polypharmacy and its consequences. Nevertheless, we preferred to analyze qualitatively the prescribed medications rather than to systematically report the prevalence of medication errors, DDI and inappropriate medication use to get an insight into the consequences of polypharmacy in multimorbid chronic pain patients. This highlights also how significant DDI could be regardless of their actual prevalence and helps instigate awareness on the harmful effects of DDI in this group.

CONCLUSION

Multimorbidity and polypharmacy are highly prevalent in elderly outpatients with chronic pain receiving home care. Regular monitoring and evaluation of medications in this population appears thus important together with strategies aiming to optimize therapy by addressing differential aspects of medication-related problems including drug interactions, overprescribing as well as underuse.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because data are archived in the Institute of Clinical Pharmacology and Toxicology, Charité – Universitätsmedizin Berlin, and can be accessed by all interested researchers on site. Requests to access the datasets should be directed to RK, reinhold.kreutz@charite.de.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the local ethical committee of the Charité-Universitätsmedizin Berlin (EA1/368/14). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Study design and concept: DD, RK, AB, AW, JS, and EA. Analysis: JS, EA, and RK. All authors participated in the interpretation of the results, drafting, and reviewing the manuscript, and approved the final version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.686990/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Electronic Supplementary Material

SUPPLEMENTARY TABLE 1 | Prescribed drug classes according to ATC code in elderly receiving home care (N = 353).

	Drug class	ATC code	Drugs, N (%)
1	Analgesics	N02	406 (11.24 %)
2	Diuretics	C03	250 (6.92 %)
3	Antithrombotics	B01	232 (6.42 %)
4	Renin-angiotensin system blockers	C09	231 (6.40 %)
5	Drugs for acid related disorders	A02	200 (5.54 %)
6	Antidiabetics	A10	189 (5.23 %)
7	Beta blockers	C07	181 (5.01 %)
8	Lipid lowering agents	C10	141 (3.90 %)
9	Vitamins	A11	138 (3.82 %)
10	Laxatives	A06	137 (3.79 %)
11	Psychoanaleptics	N06	130 (3.60 %)
12	Drugs for obstructive airway diseases	R03	113 (3.13 %)
13	Calcium channel blockers	C08	108 (2.99 %)
14	Psycholeptics	N05	100 (2.77 %)
15	Antiepileptics	N03	96 (2.66 %)
16	Antianaemics	B03	91 (2.52 %)
17	Thyroid therapy	H03	91 (2.52 %)
18	Topical drugs for muscle and joint pain	M02	75 (2.08 %)
19	Non-steroidal anti-inflammatory drugs	M01	66 (1.83 %)
20	Ophthalmics	S01	65 (1.80 %)
21	Cardiac therapy	C01	50 (1.38 %)
22	Dietary supplements	V06	50 (1.38 %)
23	Antigout preparations	M04	48 (1.33 %)
24	Drugs for functional gastrointestinal disorders	A03	40 (1.11 %)
25	Mineral supplements	A12	40 (1.11 %)
26	Antiparkinsonism drugs	N04	40 (1.11 %)
27	Urological drugs	G04	39 (1.08 %)
28	Systemic Corticosteroids	H02	28 (0.78 %)
29	Antihypertensives	C02	24 (0.66 %)
30	Drugs for bone diseases	M05	24 (0.66 %)
31	Others[a]	-	189 (5.23 %)
	Total	-	3612 (100 %)

[a]Drugs accounting for less than 20 prescriptions.

SUPPLEMENTARY TABLE 2 | List of clinically relevant drug-drug interactions in *ACHE* (N = 353) with their potential risks and recommended interventions.

Interacting drugs[a]	Number of patients affected by the interaction	Potential risks	Mechanism	Management	Severe DDI
Anticoagulants					
Rivaroxaban + citalopram (SSRI) or duloxetine (SNRI)	2	Citalopram or duloxetine may potentiate the risk of bleeding in patients treated with anticoagulants.	SSRIs and SNRIs alter platelet function and may induce bleeding because serotonin released by platelets plays an important role in hemostasis.	Monitor for clinical and laboratory signs for hematologic complications; consider prophylactic treatment with proton pump inhibitors to reduce gastrointestinal bleeding risk; consider use of other antidepressant drugs e.g., mirtazapine, trazodone, bupropion.	
Rivaroxaban + clopidogrel	1	Combination of two antithrombotic drugs (anticoagulant and platelet inhibitor) increases bleeding risk.	Added effect of two antithrombotic drugs.	The benefit-risk for each individual patient should be assessed, monitor carefully for bleeding events.	
Phenprocoumon + omeprazole or esomeprazole	3	Increased anticoagulant activity of phenprocoumon. INR increases were reported, and dose reduction was required in individual cases.	Omeprazole and esomeprazole may reduce the clearance of phenprocoumon due to competitive inhibition of its degradation.	Monitor INR with concomitant use and after discontinuation of omeprazole or esomeprazole.	

Phenprocoumon + allopurinol	3	Increased phenprocoumon plasma level and possible increase in INR doubling the risk of bleeding.	Allopurinol reduces the elimination of phenprocoumon by inhibiting its metabolism.	Monitor INR with concomitant use and after discontinuation of allopurinol.	
Phenprocoumon + sertraline, citalopram or escitalopram (SSRI)	4	SSRIs may potentiate the risk of bleeding in patients treated with anticoagulants.	SSRIs alter platelet function and may induce bleeding because serotonin released by platelets plays an important role in hemostasis.	Monitor for clinical and laboratory signs for hematologic complication; consider prophylactic treatment with proton pump inhibitors to reduce gastrointestinal bleeding risk; consider use of other antidepressant drugs e.g., mirtazapine, trazodone, bupropion.	
Phenprocoumon + metformin	3	Metformin reduces the AUC of phenprocoumon up to 63 % and increases dose requirements.	Unclear; metformin may increase phenprocoumon clearance by either enhancing liver perfusion or bile salt excretion resulting in a faster elimination of phenprocoumon.	Monitor INR with concomitant use and after discontinuation of metformin; adjust carefully phenprocoumon dosage.	
Phenprocoumon + mirtazapine	1	Prolongation of clotting time and increased risk of bleeding.	Mirtazapine can decrease the metabolism of phenprocoumon.	Monitor INR carefully; switch to another antidepressant if necessary.	
Warfarin + spironolactone	1	Spironolactone may attenuate anticoagulation effects of warfarin especially with high doses.	Unclear.	Monitor INR with concomitant use and after discontinuation of spironolactone.	

Warfarin + allopurinol	1	Prolongation of warfarin half-life and enhancement of its anticoagulant effect.	Allopurinol may inhibit the metabolism of warfarin.	Monitor INR with concomitant use and after discontinuation of allopurinol.	
Warfarin + tramadol	1	Increase in INR and risk of bleeding; more frequent in carriers of the slow CYP2D6 allele.	Unclear; possibly related to reduced activity of CYP2D6 by tramadol.	Monitor INR with concomitant use and after discontinuation of tramadol; dose reduction of warfarin to 70 % may be necessary.	
Enoxaparin + ASA[b]	1	Combination of two antithrombotic drugs (anticoagulant and platelet inhibitor) increases bleeding risk.	Added effect of two antithrombotic drugs.	Use cautiously only when necessary, with close clinical and laboratory observation for bleeding complications and neurological impairments.	✓
Apixaban, rivaroxaban or edoxaban + ibuprofen[c]	5	Increased risk of bleeding.	NSAIDs inhibit platelets and increased gastrointestinal bleeding risk and can increase exposure to anticoagulants eliminated by renal clearance by acute kidney injury.	Avoid use of NSAIDs in elderly patients with high risk of bleeding; reduce other modifiable bleeding risk factors.	
Apixaban or rivaroxaban + ASA[b]	2	Combination of two antithrombotic drugs (anticoagulant and platelet inhibitor) increases bleeding risk.	Added effect of two antithrombotic drugs.	Use cautiously only when necessary, with close clinical and laboratory observation for bleeding complications and neurological impairments.	✓

Rivaroxaban + oxcarbazepine	1	Oxcarbazepine decreases the plasma concentrations of rivaroxaban and increases the risk of therapeutic failure and thrombosis.	Oxcarbazepine induces CYP3A4 for which rivaroxaban is a substrate.	Avoid use; consider alternative antithrombotic drug (e.g., warfarin).	✓
Phenprocoumon + L-thyroxine	4	L-thyroxine may increase the risk of bleeding at initiation of therapy.	L-thyroxine increases the metabolism of vitamin K-dependent coagulation factors; not specific for phenprocoumon but all anticoagulants including with similar mechanism of action.	Titrate the dose slowly; monitor INR or prothrombin time when initiating, discontinuing, or changing the dosage of L-thyroxine in stabilized patients and adjust dose accordingly.	✓
Phenprocoumon + ibuprofen[c]	1	Increased risk of bleeding.	NSAIDs inhibit platelets and increased gastrointestinal bleeding risk and can increase exposure to anticoagulants eliminated by renal clearance by acute kidney injury.	Avoid use of NSAIDs in elderly patients with high risk of bleeding; reduce other modifiable bleeding risk factors.	
Phenprocoumon + ASA[b]	1	Increased risk of bleeding.	Added effect of two antithrombotic drugs.	Use cautiously only when necessary, with close clinical and laboratory observation for bleeding complications and neurological impairments.	✓

Warfarin + amiodarone	1	Amiodarone may increase the pharmacologic effects of warfarin.	Amiodarone inhibits CYP2C9 and CYP3A4 hepatic metabolism of S-warfarin, poor CYP2C9 metabolizers may have a higher risk of bleeding and a faster onset of the interaction.	Reduce anticoagulant dosage by 30 % to 50 %; monitor within first 7 weeks of therapy prothrombin time or INR; monitor for signs of excessive anticoagulation.	✓
Diuretics					
Loop diuretics					
Furosemide or torasemide + ACEi[d]	67	Hyponatremia and hypovolemia increase the risk of falling for elderly patients who are more prone to develop hyponatremia after age 75 years. ACEi may cause renal insufficiency or acute renal failure in patients with sodium depletion.	Co-administration increases risk of hypotension and hypovolemia than does either drug alone especially with high doses of loop diuretics.	Monitor blood pressure, renal function, and electrolytes during co-administration.	
Furosemide or torasemide + digitalis glycosides	8	Increased risk for digitalis-induced arrhythmias.	Diuretic-induced hypokalemia and hypomagnesemia.	Monitor for potassium and magnesium levels; check for signs of possible digoxin toxicity or electrolyte disturbances; adjust digitalis dose.	✓

Thiazide diuretics/thiazide-like diuretics					
HCT, xipamide or indapamide + digitalis glycosides	4	Increased risk for digitalis-induced arrhythmias.	Diuretic-induced hypokalemia, hypomagnesemia and hypercalcemia.	Monitor potassium, magnesium and calcium levels; check for signs of possible digoxin toxicity or electrolyte disturbances; adjust digitalis dose.	✓
HCT, xipamide or indapamide + ACEi[d]	28	Hyponatremia and hypovolemia increase the risk of falling for elderly patients who are more prone to develop hyponatremia after age 75 years. ACEi may cause renal insufficiency or acute renal failure in patients with sodium depletion.	Thiazide-induced water and sodium depletion increase the risk of hypotension and hypovolemia when co-administered with ACEi especially with high doses of thiazide diuretics.	Monitor blood pressure, renal function and electrolytes during co-administration.	
Potassium-sparing diuretics					
Spironolactone, eplerenone, triamterene or amiloride + RAS blockers	24	Increased the risk of hyperkalemia in patients with risk factors such as renal impairment, diabetes, old age, severe or worsening heart failure, and concomitant use of potassium supplements.	RAS blockers increase serum potassium which could be additive with that induced by potassium-sparing diuretics.	Use with caution; monitor closely for signs of hyperkalemia; check renal function regularly; avoid potassium supplementation.	✓
Statins					
Simvastatin (30, 40 mg) + amlodipine	4	Higher risk of statin-induced myopathy.	Amlodipine inhibits simvastatin metabolism via intestinal and hepatic	Simvastatin dosage should not exceed 20 mg daily when	✓

			CYP3A4 resulting in higher plasma concentrations of simvastatin and its active metabolite simvastatin acid.	used in combination with amlodipine.	
Simvastatin (20 mg) + amlodipine	4			Avoid co-administration at the same time; separate dosing by at least 4 h.	
Simvastatin + dabigatran	2	Simvastatin increases the risk of bleeding associated with the use of dabigatran by 44 %.	Via P-gp inhibition of simvastatin and increase in dabigatran-etexilate absorption.	Avoid co-administration; switch to another statin other than simvastatin or lovastatin.	✓
Simvastatin + carbamazepine	1	Carbamazepine decreases AUC of simvastatin by 25 % and its active metabolite simvastatin acid by 18 %.	Carbamazepine induces the metabolism of simvastatin and simvastatin-acid via intestinal and hepatic CYP3A4.	Increase the dosage of simvastatin, switch to other statins such as pravastatin metabolized by non-CYP routes, and rosuvastatin with lower metabolic fraction.	✓
Simvastatin + warfarin	1	Simvastatin enhances the anticoagulant response to warfarin depending on the CYP2C9 genotype, reduces dosage requirement of warfarin by 29 % in carriers of the slow metabolizing allele (CYP2C9*3) and by 43 % in homozygous carriers.	Possibly due to selective inhibition of CYP2C9*3 allele by simvastatin.	Closer monitoring of INR, switch to another statin not affecting anticoagulation such as pravastatin.	
Simvastatin + phenytoin	1	Phenytoin reduces the lipid lowering efficacy of simvastatin.	Phenytoin induces CYP enzymes including CYP3A4 isoenzyme thus increasing the metabolism of simvastatin.	Adjust dose of simvastatin; monitor cholesterol levels especially with familial hypercholesterolemia due to higher cardiovascular risk.	✓

Simvastatin + sacubitril /valsartan	1	Sacubitril may increase the plasma concentrations of simvastatin increasing the risk of statin-induced myopathy.	Sacubitril inhibits hepatic uptake transporters OATP1B1 and/or OATP1B3 to which statin are substrate.	Monitor for signs of myopathy or rhabdomyolysis.	
Simvastatin + dronedarone	1	Dronedarone increases the plasma concentrations of simvastatin and metabolite simvastatin acid increasing the risk of statin-induced myopathy.	Dronedarone inhibits both intestinal P-gp and hepatic/intestinal CYP3A4 isoenzyme enhancing absorption as well as reducing simvastatin and simvastatin acid clearance.	Adjust dose; monitor for signs of myopathy or rhabdomyolysis; switch to other non P-gp/CYP3A4 substrates e.g., fluvastatin, pitavastatin, or rosuvastatin.	✓
Simvastatin + colchicine	1	Increased risk of myopathy and rhabdomyolysis by pharmacodynamic and pharmacokinetic interactions.	Both drugs are myotoxic and may have additive or synergistic effects when used together. Both are P-gp/CYP3A4 substrates, competitive inhibition may occur resulting in increased drug absorption and decreased excretion.	Monitor for signs of myopathy or rhabdomyolysis; monitor creatine kinase level after co-administration and after any dose increase.	✓
Simvastatin + ranolazine	1	Ranolazine increases the plasma concentrations of simvastatin and simvastatin-acid increasing the risk of statin-induced myopathy.	Ranolazine inhibits intestinal and hepatic CYP3A4.	Simvastatin dosage should not exceed 20 mg daily; switch to other non P-gp/CYP3A4 substrates e.g., fluvastatin, pitavastatin, or rosuvastatin.	✓

Further clinically relevant interactions demonstrated in one patient					
Amiodarone + metoprolol	-	Additive effects of severe bradycardia, hypotension, or cardiac arrest.	Amiodarone increases the AUC of metoprolol by 80 %. The extent of increased AUC depends on CYP2D6-genotype.	Avoid this combination or monitor blood pressure and ECG.	✓
Amiodarone + fentanyl	-	Increased risk for cardio-depressive effects.	Coadministration with inhibitors of CYP3A4 such as amiodarone may increase the plasma concentrations of fentanyl, which is metabolized by this isoenzyme.	Monitor for signs of fentanyl toxicity (e.g., dizziness, confusion, fainting, extreme sedation, bradycardia, shortness of breath); adjust dosage if necessary.	✓
Amiodarone + digitoxin	-	Increased risk for digitalis toxicity.	Coadministration with amiodarone may increase serum digoxin concentrations by up to 100 %, frequently resulting in clinic[al] toxicity.	Adjust dosage; monitor serum digitalis level and observe patients for clinical evidence of digitalis toxicity (e.g., nausea, anorexia, visual disturbances, slow pulse, irregular heartbeats).	✓
Metoprolol + nifedipine, *fast-acting* (on-demand)	-	Increased hypotension and risk of heart failure.	Additive cardiovascular effects.	Monitor blood pressure; use prolonged release preparations for regular use.	
Metoprolol + digitoxin	-	Increased risk for bradycardia.	Concomitant use of digitalis glycosides and beta-blockers may increase the risk of bradycardia and AV-block.	Monitor heart rate, ECG for AV block.	

DDI, drug-drug interaction; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin noradrenaline reuptake inhibitor; INR; International Normalized Ratio; AUC, area under the concentration-time curve; CYP, cytochrome P450; ASA, acetyl salicylic acid; NSAID, nonsteroidal anti-inflammatory drug; ACEi; angiotensin converting enzyme inhibitors; HCT, Hydrochlorothiazide; RAS blockers, renin angiotensin system blockers

including ACEi and angiotensin receptor blockers (ARB); P-gp, P-glycoprotein; OATP, organic anion transporting polypeptides; ECG, electrocardiogram, AV block; atrioventricular block.

[a]For the drug interaction analysis, all active ingredients in mono- and combination -preparations were considered. Some patients in *ACHE* were treated with more than one active ingredient belonging to the same drug class.

[b]ASA in 100 mg dose.

[c]Ibuprofen (400 - 600 mg) taken on-demand.

[b]This interaction applies also to ARB.

7 Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

8 Vollständige Publikationsliste

Originalarbeiten:

Budnick A, Kuhnert R, Wenzel A, Tse M, **Schneider J**, Kreutz R, Dräger D. Pain-associated clusters among nursing home residents and older adults receiving home care in Germany. *Journal of Pain and Symptom Management*. 2020 Jul;60(1):48-59. doi: 10.1016/j.jpainsymman.2020.01.018

Budnick A, Wenzel A, **Schneider J**, Paschke-Duke M, Kreutz R, Dräger D. Schmerzgeschehen bei nichtauskunftsfähigen ambulant versorgten Pflegebedürftigen – Herausforderungen und Empfehlungen. *Der Schmerz.* 2019 Dec;33(6):523-532. doi: 10.1007/s00482-019-00404-5

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