

Aus der Klinik und Poliklinik für Neurologie der Universitätsmedizin Rostock

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**Prävalenz von potenziellen
Medikamenteninteraktionen und deren Einschätzung
mithilfe verschiedener Interaktionssoftwares bei
Patienten mit Multipler Sklerose**

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Hinweis: Die in dieser Arbeit für Personen verwendete männliche Form bezieht sich immer zugleich auch ausdrücklich auf die weibliche und jede andere Geschlechteridentität.

1. Einleitung

1.1. Multiple Sklerose (MS)

Die Multiple Sklerose (MS) beziehungsweise (bzw.) Encephalomyelitis disseminata ist die häufigste chronisch-entzündliche Erkrankung des zentralen Nervensystems (ZNS) [1]. Die Pathophysiologie ist namensgebend für die Erkrankung: chronische Läsionen, die sich an unterschiedlichen Orten im ZNS manifestieren [2]. Von der demyelinisierenden, neurodegenerativen und immunmedierten Erkrankung, die sich typischerweise im jungen Erwachsenenalter erstmanifestiert [3], sind weltweit mehr als 2,8 Millionen Menschen betroffen [4]. Die globale Prävalenz ist geografisch sehr inhomogen verteilt. Europa und die USA weisen die höchsten Prävalenzraten mit 142,8 bzw. 309,2 Fällen pro 100.000 Einwohnern auf [4, 5]. Die globale Prävalenz stieg zwischen 2013 und 2020 um circa (ca.) 50% [4]. Frauen sind mehr als doppelt so häufig von MS betroffen wie Männer [6].

Die Pathogenese der Erkrankung ist bis heute nicht vollständig geklärt. Durch eine vermutete Autoimmundysregulation erfolgt eine Invasion peripherer T- und B-Lymphozyten ins ZNS, wo diese mutmaßlich von lokalen antigenpräsentierenden Zellen reaktiviert werden und entzündliche Läsionen entstehen [7, 8]. Diese Läsionen können im gesamten ZNS auftreten. Aufgrund der Inflammation kommt es zur Demyelinisierung, zum Axon- und Synapsenverlust und zur konsekutiven reaktiven Gliose [9], gefolgt von teilweiser Remyelinisierung. Bisher wurde eine Vielzahl an mit MS assoziierten Faktoren identifiziert, darunter genetische Faktoren wie HLA-Ausprägungen (HLA, humanes Leukozytenantigen), Umweltfaktoren wie Sonnenlichtexposition und Epstein-Barr-Virus (EBV)-Infektionen sowie Lifestyle-Faktoren wie Tabakkonsum [10–16].

Aufgrund der unterschiedlich verteilten Entzündungsherde, die in Gehirn und Rückenmark entstehen, ergibt sich eine individuell sehr heterogene Symptomatik [17, 18]. Die Variabilität der Symptome in multiplen Organsystemen sowie atypische Symptome können die Diagnosestellung erschweren, sodass Patienten oft zahlreiche Ärzte verschiedener Fachrichtungen aufsuchen müssen, bevor die Diagnose MS gestellt werden kann [19, 20]. Zu den häufigsten Symptomen zählen Dysästhesien, Paresen, Fatigue und Visusstörungen durch die häufig vorangehende Optikusneuritis. Auch vegetative Symptome wie Blasen- und Sexualfunktionsstörungen sowie neuropsychiatrische Defizite treten häufig auf [17, 21, 22].

Die Behinderung eines Patienten kann mit der sog. *Expanded Disability Status Scale* (EDSS) systematisch erfasst werden [23]. Dabei wird mithilfe einer Skala zwischen Null und Zehn der Behinderungsgrad quantifiziert: ein Wert von Null beschreibt den physiologischen Zustand, ein Wert von Zehn den Tod infolge einer MS. Zur Diagnose einer MS werden die McDonald-Kriterien verwendet [24], in die sowohl klinische als auch paraklinische Befunde sowie laborchemische Liquoruntersuchungen eingehen. Mithilfe der Magnetresonanztomographie können Läsionen des ZNS dargestellt und deren zeitliche und örtliche Dissemination eingeschätzt werden [25], was neben der Symptomatik eine wesentliche Rolle für die Einschätzung des Krankheitsverlaufes spielt. Es werden drei Hauptverlaufsformen der MS unterschieden [26]: die sogenannte (sog.) schubförmig remittierende MS (*relapsing-remitting MS*, RRMS), die primär progrediente MS (*primary progressive MS*, PPMS) und die sekundär progrediente MS (*secondary progressive MS*, SPMS). Als mögliche Vorstufe der MS gelten das radiologisch isolierte Syndrom (RIS) sowie das klinisch isolierte Syndrom (*clinically isolated syndrome*, CIS) [27]. Die RRMS ist die häufigste Verlaufsform, von der initial 85-90% aller Patienten betroffen sind. Sie ist durch das Auftreten von sog. Schüben, also dem Neuauftreten von Symptomen bzw. die Verschlimmerung bestehender Symptome, die sich meist innerhalb von Tagen entwickeln und vollständig oder unvollständig wieder zurückbilden, charakterisiert [24]. Bei einem bis drei Prozent der Patienten mit RRMS wird jährlich eine sich daraus entwickelnde SPMS diagnostiziert [28]. Bei dieser besteht nach vorherigem schubförmigem Verlauf eine progrediente Zunahme der Behinderung. Aufgesetzte Schübe sind zusätzlich möglich. Die Diagnose SPMS wird in den meisten Fällen retrospektiv gestellt [26]. Bei der PPMS besteht von Beginn der Erkrankung an eine progrediente Behinderungszunahme ohne wesentliche Remission und ohne auftretende Schübe [26].

Eine kurative Behandlung der MS ist derzeit nicht möglich, jedoch gibt es verschiedene Säulen der Therapie. Medikamentöse Therapiesäulen sind die symptomatische, die verlaufsmodifizierende und die akute Schubtherapie. Zur akuten Schubtherapie werden hochdosierte Glucocorticosteroide bzw. bei Ausbleiben eines Therapieerfolgs die Plasmaseparation oder Immunadsorption angewandt [29]. Die verlaufsmodifizierende Therapie ist je nach Verlaufsform unterschiedlich. Medikamente für diese Therapiesäule werden als sog. *disease-modifying drugs* (verlaufsmodifizierende Medikamente, DMDs) bezeichnet. Es gibt verschiedene immunmodulierende und -supprimierende Wirkstoffe, die vor allem bei der RRMS und SPMS angewendet werden [30], mit dem Ziel, neue

Läsionen und Schübe zu verhindern und die Behinderungsprogression zu verlangsamen. Bei der PPMS sind die Therapiemöglichkeiten stark begrenzt, da hierfür momentan nur ein zugelassenes DMD zur Verfügung steht (Ocrelizumab) [30–32]. Die nichtmedikamentöse Therapie umfasst neben Physio-, Psycho- und Ergotherapie verschiedene *Coping*-Strategien, das heißt (d. h.) Strategien zum Umgang mit der eigenen Erkrankung und den daraus resultierenden Anforderungen [33].

Aufgrund der interindividuell sehr heterogenen Symptomatik und Krankheitsprogression ist eine Prognose des langfristigen Krankheitsverlaufs und des Ansprechens auf Therapien nur schwer abschätzbar. Mit einem eher günstigen Verlauf der Erkrankung assoziierte Faktoren sind unter anderem (u. a.) ein junges Erkrankungsalter (vor dem 35. Lebensjahr), ein monosymptomatischer Beginn der MS und eine gute Remission nach dem ersten Schub [1]. Die Lebenserwartung gegenüber der Allgemeinbevölkerung ist um durchschnittlich 7 Jahre reduziert [34].

1.2. Polypharmazie (PP)

Polypharmazie (PP) ist nach der in wissenschaftlichen Arbeiten am meisten verwendeten Definition die gleichzeitige Einnahme von \geq fünf Medikamenten [35]. Sie betrifft aus unterschiedlichen Gründen einen zunehmenden Teil der Bevölkerung [36, 37]. Einerseits werden Menschen immer älter und durch die im Alter zunehmende Multimorbidität steigt auch der Bedarf an Medikation. Andererseits steigt die Anzahl der verschriebenen Medikamente, u. a. durch neue Therapiemöglichkeiten, stetig an [38]. Durch PP erhöht sich wiederum das Risiko, Medikamenteninteraktionen (*drug-drug interactions*, DDIs) zu erleiden [38], aber auch ein erhöhtes Risiko für Therapie-Non-Adhärenz [39] sowie vermehrte Nebenwirkungen und eine erhöhte Hospitalisierungsrate sind damit verbunden [40].

PP ist nicht einheitlich definiert. Es existieren mehr als 100 verschiedene Definitionen [35]. Bei der gängigsten Definition werden alle applizierten Medikamente betrachtet (totale PP) [35], also sowohl verschreibungspflichtige (Rx) als auch nicht verschreibungspflichtige Medikamente (*over-the-counter*, OTC). Eine andere Definition beschreibt die sog. verschriebene PP (Rx-PP), die als erfüllt gilt, sobald vom Patienten \geq fünf Rx-Medikamente gleichzeitig eingenommen werden [41]. Einer Studie des Robert-Koch-Instituts (RKI) aus dem Jahr 2013 zufolge betrug die Prävalenz von PP in Deutschland bei 70- bis 79-Jährigen Männern und Frauen 47% bzw. 53,2% [41]. Derselben Quelle nach lag in dieser Gruppe der

Anteil der von Rx-PP betroffenen Männer und Frauen bei 9,9% bzw. 13,6%. Daten zur Prävalenz von PP in der allgemeinen und vor allem jüngeren Bevölkerung sind begrenzt, da dieser Aspekt aufgrund der für sie hohen klinischen Relevanz hauptsächlich bei älteren und multimorbiden Patienten untersucht wurde. In einer schwedischen Studie aus dem Jahr 2020 wurde der Anteil der Allgemeinbevölkerung, der im Jahr 2014 von totaler PP betroffen war, mit 19% angegeben [36].

1.3. Potenzielle Medikamenteninteraktionen (pDDIs)

Potenzielle Medikamenteninteraktionen (*potential drug-drug interactions*, pDDIs) können als klinisch relevante Veränderungen in Pharmakokinetik (PK) und/oder -dynamik (PD) simultan eingenommener Medikamente verstanden werden [42]. Unter PK werden die Auswirkungen aller Prozesse im Organismus verstanden, denen ein Wirkstoff unterliegt, unter PD reziprok die Auswirkungen des Wirkstoffes auf den Organismus [43]. Da PK und PD interindividuell unterschiedlich sein können [44], ist häufig die Rede von *potenziellen* Medikamenteninteraktionen, die nicht obligat bei jedem Patienten auftreten und in ihrer Stärke unterschiedlich ausgeprägt sein können. Das macht das Auftreten und die Ausprägung tatsächlicher DDIs schwer vorhersehbar. Auswirkungen von DDIs können eine Verstärkung oder Abmilderung der Wirkung mindestens eines der eingenommenen Medikamente sein, was, in Abhängigkeit der Grunderkrankung, zu Nebenwirkungen bis hin zu lebensbedrohlichen Komplikationen führen kann [45–47].

Einen relevanten Einfluss auf pharmakokinetische Prozesse haben verschiedene Enzyme, die u. a. an der Verstoffwechslung von Pharmaka beteiligt sind, beispielsweise (bspw.) die CYP-Enzyme (Cytochrome P450). Das relevanteste dieser Gruppe, CYP3A4, wird durch zahlreiche Substanzen induziert bzw. inhibiert. Dies wirkt sich stark auf die Plasmaspiegel der durch dieses Enzym metabolisierten Substrate aus und kann leicht zu einer erhöhten Toxizität, aber ebenso Wirkabschwächung führen. Ein konkretes Beispiel hierfür wäre die Inhibition von CYP3A4 durch das Antibiotikum Clarithromycin, wodurch der Wirkstoffspiegel des CYP3A4-Substrates Simvastatin erheblich steigen würde. Als Folge kann eine potenziell letale Rhabdomyolyse auftreten [48].

Aufgrund von komplexem Medikationsmanagement und mangelnder Vernetzung bzw. Austausch verschiedener Fachärzte sind pDDIs weiterhin ein unterschätztes Problem [49, 50]. In einem systematischen Review konnte gezeigt werden, dass ca. ein Prozent aller Krankenhauseinweisungen weltweit aufgrund von DDIs und deren Auswirkungen

erfolgt [51]. Dies betont die Relevanz des Themas und deutet den finanziellen Aspekt der Problematik von pDDIs bzw. daraus resultierend DDIs an [52, 53]. Zur vereinfachten Detektion von pDDIs wurden sog. *clinical decision support softwares* (CDSS) bzw. *drug-drug interaction databases* (DDID) entwickelt. Da es mit der stetig steigenden Zahl zugelassener Medikamente [54] zunehmend komplexer wird, die pDDIs von Patienten zu überblicken, sind mittlerweile verschiedene solcher Softwares entwickelt worden [55]. Das Prinzip der meisten dieser Anwendungen ist ähnlich: einzelne Wirkstoffe oder Medikamente, teilweise auch Nahrungs- und Genussmittel wie Kaffee und Tabak, werden eingegeben, woraufhin daraus entstehende pDDIs angezeigt und nach Schweregrad klassifiziert werden. Mit diesen Informationen können je nach Datenbank auch Aussagen über potenzielle Medikamenten-Nahrungsmittelinteraktionen (*potential drug-food interactions*, pDFIs) getroffen werden. Mithilfe der durch die Software erfolgten Einschätzung kann der Arzt die Medikation des Patienten gegebenenfalls anpassen. Aufgrund der starken Dependenz einer pDDI von unterschiedlichen Faktoren ist die Definition von pDDIs in einzelnen Interaktionssoftwares uneinheitlich. Daraus resultieren teilweise starke Unterschiede in der Detektion sowie Einschätzung der pDDIs [56, 57]. Unter anderem durch hohe Anzahlen unbedeutender pDDIs bzw. solcher mit geringem Schweregrad kann es zu Nachlässigkeit und zu einer gewissen Ignoranz gegenüber pDDIs kommen, sodass Hinweise übergangen werden [58].

1.4. PP und pDDIs bei Patienten mit MS

Die Relevanz von PP und pDDIs für den wissenschaftlichen Diskurs der MS wird deutlich, wenn man betrachtet, dass die MS eine symptomreiche Erkrankung ist, die sich klinisch sehr variabel darstellen kann [59]. Dementsprechend werden, schon um die Symptomtherapie abzudecken, im Verlauf der Erkrankung in der Regel mehrere Medikamente benötigt [59, 60]. Hinzu kommt die kausalerorientierte Therapie der MS mit DMDs [30, 31]. Bei einem durchschnittlichen Alter der Patienten mit MS in Deutschland von ca. 46 Jahren [61] sind teilweise auch Therapeutika gegen Komorbiditäten notwendig. Die Summe aller für einen Patienten mit MS nötigen Medikamente kann daher in einem erhöhten Risiko für PP und damit für pDDIs resultieren.

Patienten mit MS sind zu Krankheitsbeginn im Vergleich zu Patienten mit anderen neurologischen oder immunologischen Erkrankungen im Durchschnitt relativ jung und stellen damit eine besondere Gruppe dar. Sie haben eine erheblich höhere Anzahl sogenannter *disability-adjusted life years* (DALY), also krankheitsbelasteter Lebensjahre,

die neben den durch die Erkrankung verlorenen Lebensjahren durch einen früheren Tod auch die insgesamt mit einer Erkrankung gelebten Jahre erfasst [62]. Verglichen mit den durchschnittlich älteren Patienten mit anderen neurologischen, chronischen Erkrankungen [63, 64] müssen durch die höhere verbleibende Lebenserwartung der Patienten mit MS langfristige Folgen der Krankheit sowie der Therapie beachtet werden. Weiterhin hat, besonders bei Frauen, die Familienplanung besondere Relevanz. Obwohl pDDIs in nicht unerheblicher Weise den Verlauf von Erkrankungen sowie die Lebensqualität von Patienten beeinflussen können [65, 66], gibt es bislang kaum Studien, die sich mit PP und/oder pDDIs bei nicht-geriatrischen Patienten wie solchen mit MS befassen.

In einer kleinen Kohorte weiblicher Patientinnen mit MS ($n=131$) konnte bisher durch die Rostocker Arbeitsgruppe eine PP-Prävalenz von 41,2% nachgewiesen werden [67]. Für diese Patientengruppe wurden auch pDDIs identifiziert. Zur Detektion von pDDIs wurde dabei die Interaktionssoftware MediQ (Kapitel (Kap.) 3.2.) verwendet [67]. Neben MediQ gibt es weitere Interaktionssoftwares, mit Hilfe derer die Medikation von Patienten hinsichtlich bestehender pDDIs überprüft werden kann. Es fehlen jedoch bisher Vergleiche mehrerer CDSS/DDIDs, besonders hinsichtlich der Medikation bei Patienten mit MS, um Unterschiede zwischen diesen Softwares zu identifizieren und somit deren Nutzen für die klinische Anwendung durch behandelnde Ärzte und Apotheker einzuschätzen. Um die Frage nach der Vergleichbarkeit sowie den Limitierungen verschiedener CDSS/DDID näherungsweise zu beantworten, sind daher vergleichende Untersuchungen dieser Interaktionssoftwares nötig. Besonders für Patienten mit einem hohen Medikationsbedarf, wie es MS-Patienten sind, ist eine verlässliche Interaktionssoftware von Bedeutung, um bei einer hohen Zahl simultan eingesetzter Medikamente das Risiko von pDDIs entsprechend einschätzen und minimieren zu können. Eine adäquate Identifikation von pDDIs sowie deren Schweregraden könnte dazu beitragen, zukünftig die medikamentöse Therapie von Patienten mit MS sicherer zu gestalten.

2. Fragestellungen

Ziel dieser Arbeit war es, mithilfe von drei verschiedenen Online-Interaktionssoftwares die Prävalenzen und Schweregrade von pDDIs, die bei der medikamentösen Behandlung von Patienten mit MS vorkommen können, zu erforschen. Dies erfolgte unter Berücksichtigung der Medikationslast in einer Kohorte von Patienten mit MS. Die Patienten wurden in die Subgruppen Patienten mit PP (*patients with polypharmacy*, PwP) und Patienten ohne PP (*patients without polypharmacy*, Pw/oP) unterteilt. Polypharmazie wurde als totale PP, d. h. als Einnahme von mindestens fünf Medikamenten jeglicher Art, bzw. Rx-PP, d. h. als Einnahme von mindestens fünf verschreibungspflichtigen Medikamenten, erfasst.

Eine Gegenüberstellung von totaler PP und Rx-PP und deren Assoziation zu pDDIs war ein Schwerpunkt der vorliegenden Arbeit.

- Wie hoch ist die Prävalenz von PP (totale PP bzw. Rx-PP) bei MS-Patienten?
- Wie hoch ist der Anteil an MS-Patienten, bei denen pDDIs auftreten?
- Wie sind die Interaktionen anteilig nach Schweregraden klassifiziert?
- Wie viele pDDIs, stratifiziert nach Schweregraden, können im Mittel bei Patienten mit PP identifiziert werden?

Detektierte pDDIs sollten weiterhin näher analysiert werden. Dafür stand u. a. eine Differenzierung der Zusammensetzung der pDDIs aus Rx- und OTC-Präparaten im Fokus dieser Arbeit. Ein weiteres Ziel war es, mithilfe der Interaktionssoftwares Drugs.com und Stockley's Interactions Checker (im Folgenden abgekürzt als Stockley's) neben pDDIs auch pDFIs zu identifizieren und näher zu beschreiben.

- Welche Wirkstoffe führen am häufigsten zu pDDIs und welche pDDIs treten am häufigsten bei MS-Patienten auf?
- Zu welchem Anteil sind Rx- bzw. OTC-Präparate Bestandteil von pDDIs?
- Welche klinischen, soziodemographischen und pharmakologischen Faktoren sind mit dem Auftreten von pDDIs bei Patienten mit MS assoziiert?
- Welche Wirkstoffe sind an pDFIs beteiligt und werden diese Wirkstoffe häufiger von PwP als von Pw/oP verwendet?
- Wie viele der identifizierten pDFIs sind mit einem hohen Schweregrad klassifiziert und welche Nahrungs- und Genussmittel sind am häufigsten an pDFIs beteiligt?

Ein weiterer Aspekt dieser Arbeit war der Vergleich der drei Interaktionssoftwares MediQ, Drugs.com und Stockley's hinsichtlich Detektion und Bewertung von pDDIs.

- Wie viele pDDIs können jeweils mit den drei verwendeten CDSS/DDIDs ermittelt werden und welche Überlappungen gibt es bei der pDDI-Identifizierung zwischen den Interaktionssoftwares?
- Gibt es hinsichtlich der Klassifizierung von pDDIs nach Schweregrad Unterschiede zwischen den CDSS/DDIDs?
- Gibt es pDDIs, die nach allen drei CDSS/DDIDs als schwer klassifiziert werden?

3. Methodik

3.1. Datenerhebung

Die im Rahmen dieser Arbeit durchgeführten Untersuchungen basierten auf Daten, die zwischen März 2017 und Mai 2020 in der Klinik und Poliklinik für Neurologie der Universitätsmedizin Rostock sowie im Ökumenischen Hainich Klinikum Mühlhausen erhoben wurden. In die Querschnittstudie wurden insgesamt 627 Patienten mit CIS oder MS eingeschlossen. Diese Kohorte stellte die gemeinsame Grundlage für die in den drei Publikationen beschriebenen Analysen dar. Jeder Patient wurde vor der Erfassung der Daten über das Projekt aufgeklärt und das Einverständnis zur Verarbeitung und Nutzung der Patientendaten (unter Berücksichtigung der Datenschutzbestimmungen) wurde eingeholt. Die Studie wurde von der Ethikkommission der Universität Rostock sowie von der Ethikkommission Thüringens genehmigt (Registriernummern A 2014–0089A und 2019–0048) und gemäß der Deklaration von Helsinki durchgeführt.

Folgende Einschlusskriterien waren Voraussetzungen für die Teilnahme der Patienten an der Studie: Alter von ≥ 18 Jahren sowie Diagnose eines CIS bzw. einer MS anhand der revidierten McDonald-Kriterien [24].

Das Vorgehen zur Erfassung der patientenspezifischen soziodemographischen, klinischen und pharmazeutischen Daten ist in der folgenden Abbildung (Abb.) ausführlich dargestellt (Abb. 1). Die Krankheitsdauer wurde am Zeitpunkt der Diagnosestellung bemessen. Unter Berücksichtigung aller Wirkstoffe, die die Patienten zum Zeitpunkt der Befragung einnahmen, wurden auch aufgrund akuter Beschwerden nur zeitweise eingenommene Wirkstoffe, zum Beispiel (z. B.) Antibiotika, eingeschlossen. Außerdem wurden homöopathische Mittel, Phytotherapeutika und Naturheilmittel erfasst.

MS-Patienten ($n=627$):

- Strukturiertes Interview

Soziodemografie:	Pharmazie:	Klinik:
-Alter	-Handelsname	-Behinderungsgrad
-Geschlecht	-Wirkstoff	anhand des EDSS-Scores
-Bildungsstand	-Indikation	-MS-Verlaufsform
-Ausbildung	-Einnahmeintervall	-Komorbiditäten
-Berufliche Situation	-Dosierung	-Krankheitsdauer
-Familienstand	-Applikationsform	-Behandlungssituation
-Wohnort	der eingenommenen	
-Anzahl der Kinder	Medikamente	
-Anzahl der Geschwister		

Stratifizierung der Medikamente nach:

- Therapieziel: DMD/Medikament für Komorbiditäten/Symptomtherapeutikum

Analyse der Medikationspläne ($n=627$) in jeweils drei Interaktionssoftwares:

Stockley's

Erfassung aller pDDIs und pDFIs p. P. pro Interaktionssoftware

Statistische Analyse der pDDIs:
Häufigkeiten, Minima, Maxima, MW, SA, Mediane, OR, CI

Vergleich der drei Softwares anhand folgender Punkte:

-Verhältnis von erfassten Schweregraden und Häufigkeiten

Abb. 1: Übersicht über Erfassung und Auswertung der pDDIs bei Patienten mit MS mithilfe dreier CDSS/DDID.

CDSS, *clinical decision support system*; CI, *confidence interval*, Konfidenzintervall; DDID, *drug-drug interaction database*; MS, Multiple Sklerose; MW, Mittelwert; n , Anzahl; OR, Odds Ratio; Stockley's, Stockley's Interactions Checker; pDDI, *potential drug-drug interaction*, potenzielle Medikamenteninteraktion; pDFI, *potential drug-food interaction*, potenzielle Nahrungsmittel-Medikamenteninteraktion; p. P., pro Patient; SA, Standardabweichung

3.2. Identifikation von potenziellen Medikamenteninteraktionen

Diese Arbeit beschäftigt sich mit *potenziellen* DDIs, also pDDIs, da das klinische Auftreten von DDIs nicht erfasst wurde. Um die pDDIs aus den Medikationsdaten zu ermitteln, wurden die applizierten Medikamente eines jeden der 627 eingeschlossenen Patienten anhand der Medikationspläne, d. h. ein Plan pro Patient (p. P.), zwischen Mai 2020 und November 2020 in drei verschiedene CDSS/DDIDs eingetragen. Bei den drei Interaktionssoftwares handelt es sich um MediQ, Drugs.com und Stockley's Interactions Checker (Abb. 1).

Das Schweizer Online-CDSS MediQ ist eine für den klinischen Gebrauch durch medizinisches Fachpersonal vorgesehene Software, mit der die Risikoabschätzung einer Kombinationsbehandlung mit mehreren Medikamenten erleichtert werden soll. Neben Wirkstoffen und Medikamenten können hier personenbezogene Angaben wie genetische Faktoren, bspw. Polymorphismen der Cytochrom-P450-Enzyme oder HLA-Ausprägungen, und konsumierte Nahrungs- und Genussmittel (z. B. Tabak und Alkohol) eingegeben werden. Um diese Software zu nutzen, muss eine Lizenz erworben werden.

Drugs.com ist eine frei zugängliche, primär für Patienten entworfene englischsprachige Software, deren Ziel es ist, verständlich und patientenorientiert über Medikamente und deren mögliche Wechselwirkungen zu informieren. Es können Wirkstoffe eingegeben werden, deren potenzielle Interaktionen mit Nahrungs- und Genussmitteln ebenfalls angezeigt werden. Auf der Benutzeroberfläche kann zwischen Informationen für Patienten ohne genaue Angabe des Mechanismus einer Interaktion und einer detaillierteren Version für medizinisches Personal gewählt werden.

Stockley's Interactions Checker, im Folgenden mit „Stockley's“ abgekürzt, ist eine Datenbank, die auf einem von der *Royal Pharmaceutical Society* herausgegebenen Buch basiert [68]. Sie wurde entworfen, um Ärzte und medizinisches Fachpersonal bei klinischen Entscheidungen zu unterstützen und die Polypharmakotherapie von Patienten sicherer zu machen. Auch hier können mögliche Medikamenteninteraktionen mit bspw. Alkohol oder Tabak identifiziert werden.

Alle drei CDSS/DDIDs weisen jeweils 3 verschiedene pDDI-Schweregrade aus, die im Rahmen der Analyse einheitlich als „mild“, „moderat“ und „schwer“ bezeichnet wurden. In den Publikationen 1 und 2 wurden jeweils zwei der Softwares zur Identifizierung von pDDIs verwendet (Publikation 1: MediQ und Stockley's, Publikation 2: Drugs.com und

Stockley's). Für den Fall, dass der Schweregrad einer pDDI zwischen den beiden genutzten Softwares nicht einheitlich war, wurde ein in den Veröffentlichungen näher beschriebener Gesamt-Score bestimmt [69, 70]. Publikation 3 basiert auf einem Vergleich der Ergebnisse aller drei Softwares [71].

3.3. Statistische Analyse

Alle Patientendaten wurden pseudonymisiert mithilfe von Microsoft Excel (Version 16.49) erfasst. Zur statistischen Auswertung dienten die Programme SPSS Statistics (Version 27, IBM) und R (Version 3.6, R Foundation for Statistical Computing). Aus den erhobenen Daten wurden absolute und relative Häufigkeiten, Mittelwerte (MW), Standardabweichungen (SA), Mediane und Wertebereiche (Minima und Maxima) errechnet. Um die Assoziation zwischen pDDIs und verschiedenen Variablen zu überprüfen, erfolgten univariable binäre logistische Regressionsanalysen sowie multiple logistische Regressionsanalysen. Es wurden *odds ratios* (OR) und Konfidenzintervalle (*confidence interval*, CI) für das Risiko für (schwere) pDDIs errechnet. Für die vergleichende Analyse der gebildeten Patientensubgruppen (z. B. PwP versus (vs.) Pw/oP) konnten der zweiseitige Welch-*t*-Test und der Mann-Whitney-*U*-Test für metrische Variablen sowie der Chi-Quadrat-Test und der exakte Fisher-Test für kategoriale Variablen eingesetzt werden. Das Signifikanzniveau wurde bei $\alpha=0,05$ definiert. Zur Visualisierung wurden Balken- und Tortendiagramme mithilfe von Microsoft Excel (Version 16.49) erstellt. Es wurden Abbildungen mithilfe der R-Pakete *corrplot* und *VennDiagram* sowie der Software *Cytoscape* (Version 3.9.0) [72] erstellt. Weitere Abbildungen wurden mithilfe von Microsoft Word (Version 16.63) sowie Canva (Version 1.38) konzipiert.

4. Ergebnisse

Im Rahmen dieser Dissertation entstanden drei Originalarbeiten. Im Nachfolgenden sind die Ergebnisse in der zeitlichen Reihenfolge der Veröffentlichungen fokussiert dargestellt (Kap. 4.1., Kap. 4.2., Kap. 4.3.). Die Kohorte der MS-Patienten stellte die gemeinsame Basis für die in den einzelnen Publikationen beschriebenen Untersuchungen dar. Der Fokus der vorliegenden Arbeit lag auf den in der ersten Publikation beschriebenen Analysen (Kap. 4.1.). Im Anhang sind die Publikationen inklusive Abbildungen und Tabellen eingebunden (Kap. 8.). Das folgende Schaubild (Abb. 2) stellt eine Übersicht der Ergebnisse dar und zeigt die Zusammenhänge zwischen den Publikationen 1, 2 und 3.

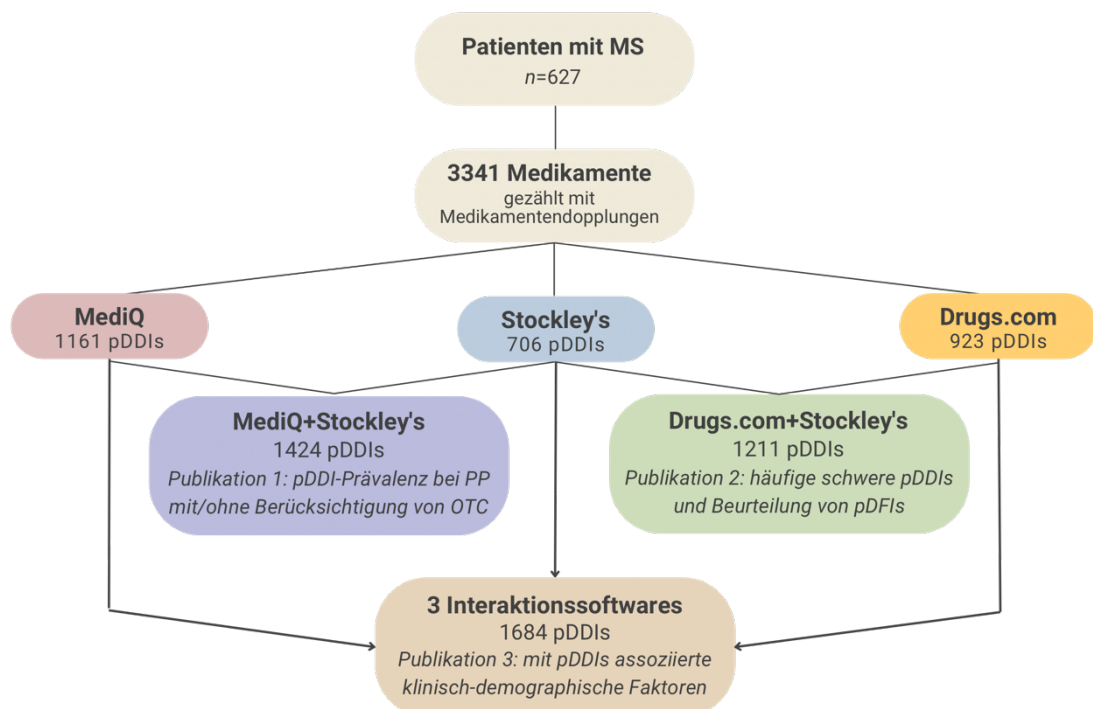


Abb. 2: Übersicht der Anzahl an detektierten pDDIs unter Verwendung von einer, zwei bzw. drei Interaktionssoftwares. Es ist die Gesamtzahl verschiedener detektierter pDDIs angegeben, d. h. ohne Dopplungen von pDDIs, falls die gleiche pDDIs bei zwei oder mehr Patienten erfasst wurde. Die farbliche Kennzeichnung dient zur besseren Übersicht.

bzw., beziehungsweise; d. h., das heißt; *n*, Anzahl; OTC, *over-the-counter*, verschreibungsfreies Medikament; pDDI, *potential drug-drug interaction*, potenzielle Medikamenteninteraktion; pDFI, *potential drug-food interaction*, potenzielle Nahrungsmittel-Medikamenteninteraktion; Stockley's, Stockley's Interactions Checker

4.1. Publikation 1: *Prevalence and severity of potential drug-drug interactions in patients with multiple sclerosis with and without polypharmacy [69]*

Von den 627 eingeschlossenen Patienten mit MS waren 70,3% weiblich und der Altersdurchschnitt lag bei 48,6 Jahren (SA: 13,3 Jahre). Im Median lag der EDSS-Score bei 3,5 und die Krankheitsdauer bei zehn Jahren. Die häufigste Verlaufsform der MS war mit 66,2% die RRMS inklusive der CIS. Kardiovaskuläre Komorbiditäten waren am häufigsten und traten bei 27,1% der Patienten auf. Durchschnittlich nahm jeder Patient 5,3 Medikamente ein (Wertebereich: 0-19), wovon durchschnittlich 4,2 Medikamente verschreibungspflichtig sowie 1,1 frei verkäuflich waren. Von allen Patienten waren 53,3% von totaler PP und 38,6% von Rx-PP betroffen. Patienten mit totaler PP bzw. jene mit Rx-PP waren mit einem Unterschied von knapp zehn Jahren signifikant älter als Patienten ohne (Rx-) PP (PwP vs. Pw/oP: 53,0 vs. 43,6 Jahre für totale PP; 54,8 vs. 44,7 Jahre für Rx-PP; *t*-Test: jeweils $p < 0,001$). Der durchschnittliche EDSS-Score sowie die mittlere Anzahl an Komorbiditäten waren bei Patienten mit totaler PP wie auch bei Rx-PP signifikant höher als bei Patienten ohne totale PP/Rx-PP (jeweils $p < 0,001$). Die Anzahl der Komorbiditäten lag p. P. zwischen Null und Neun.

Insgesamt wurden von den 627 Patienten 3341 Medikamente eingenommen, inklusive mehrfach gezählter Präparate. Von allen Arzneimitteln waren 85,5% dauerhaft bzw. 14,5% bei Bedarf verabreichte Medikamente, 78,7% der applizierten Medikamente waren verschreibungspflichtig bzw. 21,3% OTC-Medikamente. Pw/oP nahmen anteilmäßig mehr OTC-Medikamente ein als PwP, wohingegen bei PwP der Anteil der Rx-Medikamente höher war als bei Pw/oP (exakter Fisher Test: $p = 0,011$ für totale PP, $p < 0,001$ für Rx-PP). Circa 16% aller verabreichten Medikamente waren DMDs. Das am häufigsten verordnete immunmodulatorische Medikament zur Therapie der MS war Methylprednisolon, welches 19,6% der Patienten entweder zur akuten Schubtherapie oder als zyklische Dauertherapie erhielten. Applizierte Medikamente bestanden bei Pw/oP anteilig zu einem größeren Teil aus DMDs als bei PwP (Pw/oP: 31,1% totale PP; 24,0% Rx-PP vs. PwP: 11,5% totale PP; 10,8% Rx-PP). Unabhängig vom PP-Status bildeten Medikamente für Komorbiditäten stets den größten Anteil aller eingenommenen Medikamente.

Für alle 627 Patienten wurden mit den DDIDs MediQ und Stockley's insgesamt 2887 pDDIs (gezählt mit Wiederholungen) bzw. 1424 verschiedene pDDIs festgestellt (Abb. 2). Bei

36,2% aller Patienten wurde keine pDDI identifiziert. Die Anzahl an p. P. detektierten pDDIs reichte von Null bis 65, mit einem Mittelwert von 4,6 pDDIs. Bei PwP wurden im Durchschnitt deutlich mehr pDDIs identifiziert als bei Pw/oP (totale PP: $8,2 \pm 10,7$ vs. $0,5 \pm 1,0$ pDDIs p. P.; Rx-PP: $10,5 \pm 10,4$ vs. $0,9 \pm 1,4$ pDDIs p. P.). Mehr als 95% aller pDDIs entfielen auf PwP (totale PP). In der Untergruppe von Patienten mit Rx-PP wurden 88,3% aller pDDIs detektiert. Die Mehrheit aller pDDIs (65,4%) wurde als mild und nur 0,2% aller pDDIs wurden als schwer eingestuft. Der Großteil aller pDDIs (77,3%) setzte sich aus zwei verschreibungspflichtigen Medikamenten zusammen. Nur 3,7% aller pDDIs resultierten aus der Kombination zweier OTC-Präparate. Rx-Rx-pDDIs wurden zu 65,8% als mild eingestuft und 18,7% bzw. 11,2% als mild-moderat bzw. moderat. pDDIs bestehend aus zwei OTC-Medikamenten waren dagegen zu 86,9% als mild eingestuft. Die häufigste pDDI (Cholecalciferol – Magnesium) betraf 5,7% aller Patienten und wurde als mild eingestuft. Es konnte gezeigt werden, dass Patienten mit einer kardiovaskulären, neurologischen, orthopädischen oder psychiatrischen Komorbidität häufiger eine pDDI (jeglicher Schwere) aufwiesen als Patienten ohne diese Komorbiditäten (exakter Fisher Test: $p \leq 0,011$).

4.2. Publikation 2: *Associated factors of potential drug-drug interactions and drug-food interactions in patients with multiple sclerosis [70]*

Bei derselben Studienpopulation wie in Publikation 1 wurden insgesamt 2587 pDDIs, inklusive mehrfach gezählter, bei mehreren Patienten vorkommender pDDIs, bzw. 1211 unterschiedliche pDDIs unter Nutzung von Stockley's Interactions Checker und der DDID Drugs.com erfasst (Abb. 2, Seite 13). Die durchschnittliche Anzahl an pDDIs p. P. betrug 4,1. Auch hier war der Großteil der ermittelten pDDIs mild (57,1%). Schwere Interaktionen machten 3,4% der pDDIs aus. Bei 65,1% der Patienten wurde mindestens eine pDDI erfasst, bei 25,0% mindestens eine (moderat) schwere pDDI.

Folgende Variablen waren mit dem Auftreten mindestens einer pDDI assoziiert: ein höheres Alter (OR: 1,060 pro zusätzlichem Lebensjahr; $p < 0,001$), ein höherer EDSS-Score (OR: 1,586; $p < 0,001$), eine erhöhte Anzahl eingenommener Medikamente (OR: 2,665; $p < 0,001$), eine längere Erkrankungsdauer (OR: 1,041; $p < 0,001$) und eine erhöhte Anzahl an Komorbiditäten (OR: 2,235; $p < 0,001$). Eine höhere Anzahl absolvierter Schuljahre ging mit einem reduzierten Risiko für pDDIs einher (OR: 0,771; $p < 0,001$). Sowohl die Wahrscheinlichkeit einer pDDI jeglicher Schwere als auch die einer (moderat-)schweren pDDI wurden durch PP stark erhöht (\geq eine pDDI: OR: 27,322; \geq eine (moderat-)schwere pDDI: OR: 14,920). Bei PwP (totale PP) wurde signifikant häufiger mindestens eine pDDI jeglichen Schweregrades festgestellt als bei Pw/oP (93,1% bzw. 33,1%, $p < 0,001$). Die multiple logistische Regressionsanalyse ergab folgende prädiktive Variablen für das Vorliegen mindestens einer pDDI: Alter (OR: 1,034), Bildungsniveau (OR: 0,502), die Anzahl der eingenommenen Medikamente (OR: 2,608) und die Anzahl der eingenommenen DMDs (OR: 2,105).

In der Kohorte wurden 198 Medikamente identifiziert, die Bestandteil von pDFIs waren. Es wurden für 34 Medikamente als schwer eingestufte pDFIs ermittelt, wovon 21 durch eine Wechselwirkung mit Alkohol entstanden. Unter den 20 am häufigsten verwendeten Medikamenten war Ibuprofen als einziges Bestandteil einer als schwer eingestuften pDFI. Die pDFI zwischen Ibuprofen und Alkohol könnte jedoch bis zu 16,7% der Patienten betreffen, da dieser Anteil der Patienten Ibuprofen einnahm.

4.3. Publikation 3: *Screening for severe drug-drug interactions in patients with multiple sclerosis: A comparison of three drug interaction databases [71]*

Es wurden insgesamt 706 verschiedene pDDIs mit Stockley's, 923 pDDIs mit Drugs.com und 1161 pDDIs mithilfe von MediQ bei den 627 Patienten identifiziert (Abb. 2). Mit Stockley's wurde die quantitativ geringste Anzahl an pDDIs erfasst, aber qualitativ der höchste Anteil an als schwer eingestuften pDDIs (37,4%; ohne Wiederholungen). In MediQ wurden pDDIs im Allgemeinen mit einem geringeren Schweregrad eingeschätzt. Nur zehn pDDIs waren nach MediQ als schwer eingestuft. Mithilfe von Stockley's bzw. Drugs.com konnten 47 bzw. 23 als schwer klassifizierte pDDIs identifiziert werden, die in den jeweils anderen Datenbanken nicht verzeichnet waren. Insgesamt wurden mithilfe der drei Interaktionssoftwares 1684 verschiedene pDDIs detektiert, davon 18,9% (318 pDDIs) mit allen drei Softwares übereinstimmend. Die Schnittmenge war mit 563 verschiedenen, von beiden Softwares identifizierten pDDIs zwischen Drugs.com und MediQ am größten. Bezüglich der Schweregrade bestand die größte Übereinstimmung zwischen Stockley's und Drugs.com mit 60,0% einheitlichen Einschätzungen. Von den 1684 verschiedenen pDDIs wurden nur 3,3% in allen drei Interaktionssoftwares sowohl detektiert als auch mit demselben Schweregrad eingestuft (17,3% der Schnittmenge, also der 318 von allen Softwares detektierten pDDIs).

Bei 70,3% aller Patienten wurde wenigstens eine pDDI und bei 35,2% aller Patienten mindestens eine schwere pDDI mithilfe mindestens einer der drei Softwares festgestellt. Es wurden durchschnittlich $0,9 \pm 2,0$ schwere pDDIs p. P. identifiziert. Citalopram, Ibuprofen und Methylprednisolon waren häufig Bestandteile schwerer pDDIs. Durch logistische Regressionsanalysen wurden in univariablen Modellen verschiedene Prädiktoren für schwere pDDIs ermittelt, u. a. Alter, Krankheitsdauer und Grad der Behinderung (EDSS-Score) (OR>1, jeweils $p < 0,001$). Währenddessen wurden eine erhöhte Anzahl an abgeschlossenen Schuljahren (OR: 0,737; $p < 0,001$), ein höherer Bildungsgrad (OR: 0,698; $p = 0,001$) und eine Partnerschaft (OR: 0,632; $p = 0,014$) als protektive Faktoren identifiziert. Im multivariablen Modell verblieben Alter (OR: 1,029; $p = 0,003$), Komorbiditäten (OR: 1,196; $p = 0,029$) und die Anzahl der eingenommenen Medikamente (OR: 1,550; $p < 0,001$) signifikant mit dem Risiko für eine schwere pDDI assoziiert. Ein höheres Bildungsniveau war weiterhin ein protektiver Faktor (OR: 0,692; $p = 0,010$), ebenso wie eine Partnerschaft (OR: 0,591; $p = 0,034$).

5. Diskussion

Durch die weltweit zunehmende Lebenserwartung [73] nimmt auch die Multimorbidität, von der hauptsächlich ältere Menschen betroffen sind, stetig zu [74]. Steigende Raten von an Erkrankungen betroffenen Menschen [75] führen dazu, dass auch der Bedarf an Medikation und die Prävalenz von PP ansteigen. Neben älteren Menschen haben vor allem Menschen mit chronischen Erkrankungen wie der MS einen erhöhten Medikationsbedarf. Die daraus eventuell resultierende PP stellt ein weitreichendes Problem für Patienten, Angehörige und Ärzte dar [76, 77], aber auch für das Gesundheitssystem im Allgemeinen sowie die Volkswirtschaft. Neben einer geringeren Therapieadhärenz und damit einem reduzierten Therapieerfolg ist auch ein höheres Risiko für pDDIs eine mögliche Auswirkung [38–40]. Diese pDDIs können unterschiedlicher Natur sein, beschreiben im Allgemeinen aber die Wechselwirkung mindestens zweier Medikamente, die simultan eingenommen werden und sich gegenseitig in PD und/oder PD beeinflussen können [78]. Sowohl PP als auch pDDIs verdeutlichen die zunehmende Komplexität, die es in der Behandlung von (chronisch erkrankten) Patienten zu bewältigen gilt. In dieser Arbeit wurden die Prävalenz von PP bei Patienten mit MS sowie das Ausmaß und der Schweregrad von pDDIs mithilfe verschiedener Softwares bestimmt. Weiterhin wurden Assoziationen von soziodemographischen, klinischen und medikamentösen Parametern mit dem Risiko von PP und pDDIs erfasst.

Bis zum heutigen Stand gibt es nur wenige Studien zu PP und/oder pDDIs bei MS-Patienten. In der Literatur sind aktuell 14 Originalarbeiten zu dieser Thematik zu finden, sieben davon aus der Rostocker Arbeitsgruppe [67, 69–71, 79–88]. Unter den Studien anderer Forschungsgruppen befanden sich bislang keine groß angelegten Studien, die sich mit pDDIs und/oder pDFIs bei MS-Patienten beschäftigten. Zwar gibt es ähnliche Studien bei anderen chronischen neurologischen (bspw. M. Parkinson) oder autoimmunen Krankheitsbildern (z. B. rheumatoide Arthritis) [89–92], jedoch ist ein Vergleich der im Rahmen der vorliegenden Arbeit beschriebenen Ergebnisse (Kap. 4.1, Kap. 4.2., Kap. 4.3.) mit den Erkenntnissen dieser Studien schwierig, da Erkrankungen wie Parkinson oder Alzheimer-Demenz vor allem geriatrische Patienten betreffen [63, 64]. Der Altersdurchschnitt dieser Patienten liegt daher meist bedeutend über dem von Patienten mit MS, wie auch dem der Rostocker Kohorte [93, 94]. Im Gegensatz zur gut untersuchten Prävalenz von pDDIs und PP bei Patienten im Rentenalter gibt es also eine Datenlücke bei jüngeren Patienten, die durch chronische Erkrankungen wie der MS und eventuelle

Komorbiditäten einen erhöhten Bedarf an Medikation aufweisen. Die Notwendigkeit und Relevanz einer solchen Studie werden durch die hier beschriebenen Ergebnisse bekräftigt. Mit einem Durchschnittsalter von ca. 49 Jahren und einem Geschlechterverhältnis von ca. 70% zu 30% (weiblich zu männlich) war die hier untersuchte Patientenkohorte gut vergleichbar mit Patienten zweier großer MS-Register aus Deutschland. Dabei handelt es sich um das MS-Registers der Deutschen Multiple Sklerose Gesellschaft (DMSG) [61], in dem der Altersdurchschnitt bei 47,4 Jahren lag, und das Register des NeuroTransData-Netzwerks [95], dessen Altersdurchschnitt bei 49 Jahren lag. Der mediane EDSS-Score der hier beschriebenen Patientenkohorte betrug 3,5; im Median waren die Patienten seit 10 Jahren an MS erkrankt, was den Register-Daten ebenfalls ähnelt (DMSG: medianer EDSS-Score: 3,0; durchschnittliche Erkrankungsdauer: 10,6±8,7 Jahre; NeuroTransData: mittlerer EDSS-Score: 2,8; durchschnittliche Erkrankungsdauer: 14,3±8,9 Jahre). Die Patienten der untersuchten Kohorte litten zu 66,2% an einer RRMS (inklusive CIS), gefolgt von SPMS mit 24,6%. Damit war die RRMS im Vergleich zu den oben genannten Registern, in denen die RRMS einen Anteil von 74% bzw. 77% ausmacht, leicht unterrepräsentiert [61, 95]. In der Zusammenschau dieser Daten und aufgrund der relativ großen Kohorte von mehr als 600 eingeschlossenen Patienten kann trotzdem angenommen werden, dass die Kohorte repräsentativ ist.

Von jedem Patienten der Kohorte wurden im Durchschnitt 5,3 Medikamente verwendet, darunter 1,1 OTC- und 4,2 Rx-Medikamente. Laut einem Gesundheitsbericht des RKI von 2013 nahmen Frauen in Deutschland durchschnittlich 3,1 und Männer 2,0 Präparate ein [41]. Neuere Daten aus dem Jahr 2021 aus Deutschland zeigten eine Einnahme von durchschnittlich 2,2 regelmäßig verwendeten Medikamenten p. P. in der Allgemeinbevölkerung [96]. Damit war zwar die Anzahl der durchschnittlich eingenommenen Medikamente der MS-Patienten der zugrundeliegenden Kohorte ca. doppelt so hoch wie die der durchschnittlichen Bevölkerung. Jedoch war die Erhöhung nicht so stark, wie es eventuell bei Patienten mit einer chronischen, immunmedierten neurologischen Erkrankung zu erwarten gewesen wäre. In einer norwegischen Studie aus dem Jahr 2015 wurde eine durchschnittliche Anzahl von 5,4 eingenommenen verschriebenen Medikamenten bei Patienten mit MS festgestellt [88], was sich mit dem in dieser Arbeit gezeigten Ergebnis deckt.

Von den 627 Patienten in der hier untersuchten Kohorte waren 334 (53,3%) von PP (total) betroffen (Kap. 4.1). Dieses Ergebnis steht in Übereinstimmung mit der norwegischen

Studie zu PP bei Patienten mit MS, in der eine PP-Rate von 59% beschrieben wurde [88]. In Studien zu PP und verschiedenen Assoziationsfaktoren bei Patienten mit MS konnten Thelen *et al.* Prävalenzraten von PP zwischen 33% und 90% feststellen [73, 74]. In Betrachtung der Allgemeinbevölkerung wurde in einer Studie aus Neuseeland beschrieben, dass im Jahr 2018 fast 10% der Bevölkerung von PP betroffen waren [97]. In einer ähnlich konzipierten Studie aus Dänemark waren es 12% [98]. Aufgrund der begrenzten Studienlage und der uneinheitlichen Definition von PP ist es derzeit schwierig, aktuelle Daten zur Prävalenz von PP in der Bevölkerung in Deutschland zu finden. Dagegen gibt es zahlreiche Daten zu ebendieser Prävalenz für über 65-jährige Menschen [37, 99, 100]. Diese Datenlücke erschwert einen Vergleich bzw. die Einordnung in den aktuellen Kontext, verdeutlicht aber auch die Notwendigkeit von Forschungsaktivität auf dem Gebiet.

Von Rx-PP waren 242 (38,6%) Patienten der untersuchten Kohorte betroffen. Für die Prävalenz von Rx-PP gibt es ebenfalls nur wenige vergleichbare Daten, jedoch wurde in einer Studie des RKI bei Erwachsenen in Deutschland für Frauen eine Rx-PP-Rate von 13,6% und für Männer eine Rx-PP-Rate von 9,9% festgestellt [41]. Die Prävalenz von PP ist also unter Patienten mit MS sowohl für Rx- als auch totale PP deutlich gegenüber der der Allgemeinbevölkerung erhöht.

Je nach verwendeter Software wurden 706 (Stockley's), 923 (Drugs.com) bzw. 1161 (MediQ) verschiedene pDDIs identifiziert (Kap. 4.3.). Dabei zeigte MediQ mit weniger als einem Prozent den geringsten Anteil an schwerwiegenden Interaktionen, Stockley's mit 37,4% den höchsten. Die Einschätzung durch Drugs.com lag sowohl bezüglich der Anzahl der detektierten pDDIs als auch mit einem Anteil von 14,4% schwerwiegenden pDDIs zwischen den jeweiligen Ergebnissen von MediQ und Stockley's. Ähnliche Ergebnisse wurden bspw. von Zorina *et al.* bei einem Vergleich der CDSS MediQ und ID PHARMA CHECK beschrieben, bei dem durch MediQ eine deutlich höhere Anzahl an pDDIs detektiert wurde, die mehrheitlich mit dem geringsten Schweregrad eingeschätzt wurden [101, 102]. Dies wird auch von einer anderen Studie gestützt, in der mithilfe von MediQ im Vergleich mit vier anderen CDSS die meisten pDDIs für Patienten nach einer Nierentransplantation detektiert werden konnten [56]. In bisherigen Studien wurden mit Stockley's ähnlich viele pDDIs identifiziert wie durch andere CDSS/DDIDs, teilweise wurden basierend auf Stockley's sogar mehr pDDIs aufgelistet als auf der Basis von Drugs.com, was im Gegensatz zu den hier beschriebenen Daten steht [103, 104].

Die Überlappung an detektierten pDDIs der drei verwendeten Interaktionssoftwares betrug nur 18,9%. Von dieser Schnittmenge wurden 17,3% der pDDIs von allen drei Interaktionssoftwares mit demselben Schweregrad eingeschätzt. Dieses Ergebnis bestätigt Erkenntnisse anderer Studien. Vergleichbar ist eine Arbeit von Sancar *et al.*, in der drei Softwares verglichen wurden, darunter auch Drugs.com [105]. Zwischen diesen drei Interaktionssoftwares bestand eine Überschneidung von 18%. In anderen Studien stimmten teilweise nur 5% der mit mehreren Interaktionssoftwares detektierten pDDIs überein [106, 107]. Übereinstimmungsraten der Schweregrade verschiedener Interaktionssoftwares wurden mit 37,4% [108] bzw. 13,1% [105] beschrieben. Das verdeutlicht, wie stark die Einschätzung von pDDIs variieren kann, wenn verschiedene Softwares verwendet werden. Ursächlich für diese Inhomogenität der CDSS/DDIDs ist vermutlich vor allem die subjektive Einschätzung von pDDIs und deren Schweregraden, da keine einheitlich Definition existiert [109]. Infolgedessen sind Kriterien zur Identifikation sowie Evaluation in jeder Software anhand verschiedener Definitionen unterschiedlich festgelegt. Der Begriff *potenzielle* Medikamenteninteraktion verdeutlicht, dass das tatsächliche Auftreten einer DDI von verschiedenen Faktoren abhängig ist, darunter dem persönlichen Metabolismus, Dosis oder Applikationsform applizierter Medikamente. Welche Informationen letztlich in der Beurteilung einer pDDI berücksichtigt wurden, ist je nach Datenbank unterschiedlich. Weitere Faktoren, die Unterschiede im Datenbestand der CDSS/DDIDs bedingen könnten, sind die Zielgruppe sowie die Aktualität der Softwares. MediQ ist bspw. explizit für medizinisches Personal im klinischen Alltag entwickelt worden, wohingegen Drugs.com für den privaten Gebrauch durch Patienten und Nichtmediziner entworfen wurde. Da es für den medizinischen Laien wichtiger ist, einen Überblick zu bekommen und für ihn relevante und wirklich bedrohliche pDDIs identifizieren zu können [110, 111], werden hier eventuell weniger pDDIs ausgewiesen als durch MediQ, dafür aber mit höheren Schweregraden klassifiziert. Ärzte und Apotheker dagegen können mithilfe von MediQ eine höhere Anzahl an pDDIs detektieren, die aber im Regelfall mit einem geringen Schweregrad eingestuft sind. Unter diesen sollte der Arzt dann die für seinen Patienten tatsächlich relevanten pDDIs identifizieren können.

Hinzu kommt, dass jede der Interaktionssoftwares zwar regelmäßig, aber nicht gleichermaßen oft aktualisiert wird, um neue Studienergebnisse zu berücksichtigen. Daher kann es vorkommen, dass einige CDSS/DDIDs Medikamente und pDDIs beinhalten, die in anderen noch nicht verzeichnet sind. Die Varianz in der Detektion und Klassifikation von

pDDIs stellt durch die geringe Vergleichbarkeit ein Problem im klinischen Alltag dar. Zum aktuellen Stand und solange keine besseren Lösungen existieren, sollten daher Ärzte und Apotheker mindestens zwei geeignete Interaktionssoftwares verwenden, um möglichst wenige pDDIs zu übersehen und unterschiedliche Einschätzungen der Schweregrade zu erhalten [57, 105, 112, 113]. Die Ergebnisse verschiedener Studien zu pDDIs sollten immer unter Berücksichtigung der verwendeten Ressource(n) interpretiert werden.

In der untersuchten Kohorte trat bei 70,3% aller Patienten mindestens eine pDDI jeglicher Schwere auf (mit mindestens einer der drei Softwares detektiert) (Kap. 4.3). In einer Studie aus dem Jahr 2001, in der auf der Grundlage von Aufzeichnungen über alle in schwedischen Apotheken herausgegebenen Verordnungen eine Abschätzung der Prävalenz von pDDIs in der allgemeinen Bevölkerung erfolgte, konnte herausgefunden werden, dass in 13,6% aller Verschreibungen mindestens eine pDDI inbegriffen war [114]. In einer ähnlichen Studie aus der Türkei wurde sogar ein Anteil von 39,2% beschrieben [105]. Da diese Studien nicht auf eine bestimmte Erkrankung beschränkt waren, lässt sich daraus schließen, dass ein durchschnittlicher Patient mit MS ein ca. 2- bis 4-fach erhöhtes Risiko gegenüber anderweitig Erkrankten hat, mindestens eine pDDI aufzuweisen. Dabei ist zu bedenken, dass nur ein Teil dieser pDDIs klinisch relevant wird. Trotz des eher geringen Risikos einer schweren, klinisch relevanten DDI sollten Ärzte bei der Verschreibung von Medikamenten das stark erhöhte Risiko für pDDIs bei MS-Patienten beachten und gegebenenfalls zum Anlass für eine Umstellung des Medikamentsplans nehmen. Zukünftig sollte von ärztlicher Seite verstärkt darauf geachtet werden, potenziell interagierende Medikamente auszutauschen bzw. je nach Möglichkeit abzusetzen. Beispielsweise sind Statine typischerweise Substrate von CYP3A4 [115] und daher anfällig für Interaktionen. Eine Ausnahme bildet Pravastatin, das nicht durch CYP3A4 metabolisiert wird [116] und daher eventuell alternativ eingesetzt werden kann, wenn ein anderes, mit CYP3A4 interagierendes Medikament zwingend notwendig ist. Andere Medikamente können eventuell dauerhaft oder zeitweise abgesetzt werden, wenn ihr Nutzen das Risiko einer Interaktion nicht überwiegt. Die Zusammenarbeit verschiedener Fachdisziplinen sollte künftig verbessert werden, um für einen Patienten erforderliche Medikamente bei Bedarf präziser aufeinander abzustimmen. Dabei könnten auch regelmäßige Konsultationen von Apothekern helfen, um verschreibende Ärzte zur Vermeidung von DDIs bei der Erstellung von Medikationsplänen zu unterstützen. Bestehende Medikationspläne sollten regelmäßig

hinsichtlich pDDIs überprüft werden, auch wenn keine Änderungen daran vorgenommen wurden, da die Interaktionsdatenbanken regelmäßig aktualisiert werden.

Die am häufigsten als schwer eingestufte pDDI bestand aus Acetylsalicylsäure und Enoxaparin und betraf 21 Patienten (3,3% aller Patienten). Die Kombination dieser beiden Wirkstoffe kann zu einer erhöhten Blutungsneigung führen [117], da die Wirkstoffe als Thrombozytenaggregationshemmer (Acetylsalicylsäure) und Antikoagulans (Enoxaparin) zwar an unterschiedlichen Punkten ansetzen, aber insgesamt synergistisch wirken und beide die Blutgerinnung hemmen [118, 119]. Infolgedessen kann es zu schweren Blutungen kommen [118]. Sechs pDDIs wurden von den drei Interaktionssoftwares gleichermaßen als schwer eingestuft. Eine Auffälligkeit dabei war, dass an allen dieser sechs pDDIs der selektive Serotonin-Wiederaufnahmehemmer Citalopram beteiligt war. Damit war Citalopram das Medikament, das am häufigsten Teil einer von jeglicher Software als schwer eingestuften pDDI war. Citalopram hat u. a. durch seine Metabolisierung durch die CYP-Enzyme CYP2C19 und CYP3A4 ein relativ hohes Interaktionspotential [120]. Hinzu kommt eine mögliche Verlängerung des QT-Intervalls durch Citalopram [121]. Da diese QT-Zeit-Verlängerung ebenfalls von einer Vielzahl anderer Medikamente verursacht werden kann [122], potenziert sich das Risiko dafür bei Kombination von Citalopram mit den entsprechenden anderen Wirkstoffen. Damit könnte das gehäufte Vorkommen von Citalopram in als schwer klassifizierten pDDIs möglicherweise erklärt werden. Diese Häufung wurde auch in einer früheren Studie zu Demenzerkrankten durch eine andere Arbeitsgruppe beschrieben [123].

Von besonderer Relevanz ist der hier beschriebene Aspekt, dass der Großteil aller pDDIs (77,3%) aus der Verwendung zweier Rx-Medikamente resultierte (Kap. 4.1.). Knapp über 20% aller pDDIs enthielten allerdings mindestens ein OTC-Medikament, wodurch betont wird, dass frei verkäufliche Wirkstoffe bei der Bestimmung von pDDIs nicht vernachlässigt werden dürfen. Nicht nur die Anzahl, auch der Schweregrad der in Zusammenhang mit OTC-Präparaten detektierten pDDIs lassen die Bedeutung von OTC-Wirkstoffen bei der Überprüfung der Medikation von MS-Patienten ersichtlich werden. Bisher jedoch wurden OTC-Präparate regelmäßig bei der Evaluation von pDDIs vernachlässigt [124–126]. Hinzu kommt, dass Patienten Studien zufolge in bis zu 44% der Fälle nicht verschreibungspflichtige Wirkstoffe sowie Nahrungsergänzungsmittel bei der Frage nach eingenommenen Medikamenten nicht angeben [127, 128]. Ersichtlich wird also, dass einerseits OTC-Präparate bewusst in die Evaluation von pDDIs eingeschlossen werden sollten, und andererseits Patienten aktiv nach

den von ihnen eingenommenen OTC-Präparaten sowie Nahrungsergänzungsmitteln befragt werden müssen, um ein vollständiges Bild der pDDIs eines Patienten zu erlangen.

Die vorliegende Arbeit zeigte deutlich auf, dass ein höheres Alter, eine höhere Anzahl eingenommener Medikamente und das Vorliegen von Komorbiditäten Risikofaktoren für das Auftreten mindestens einer pDDI darstellen. In den logistischen Regressionsanalysen, die in den Publikationen 2 und 3 (Kap. 4.2. bzw. 4.3.) beschrieben sind, konnte außerdem ein höherer Behinderungsgrad, gemessen am EDSS, mit dem Auftreten von (schweren) pDDIs assoziiert werden. PP erwies sich als starker Risikofaktor für das Auftreten mindestens einer pDDI, genauer gesagt war das Risiko für das Auftreten von pDDIs für PwP um das 27-fache gegenüber Pw/oP erhöht (totale PP) (Kap. 4.2). Dieses Ergebnis stützt Erkenntnisse bisheriger, nicht MS-bezogener Studien, in denen ebenfalls eine starke Assoziation zwischen PP und dem Auftreten von pDDIs bzw. einem signifikant erhöhten Risiko für pDDIs durch eine höhere Anzahl an Medikamenten beschrieben wurde [125, 129–132]. Ähnliches gilt für weitere, in dieser Arbeit beschriebene Risikofaktoren für pDDIs. Damit untermauert die vorliegende Dissertation die Erkenntnisse sowohl früherer Studien der Forschungsgruppe Zettl als auch Ergebnisse aus Studien anderer Forschungsgruppen [83, 86, 133–135].

Es konnten weiterhin pDFIs mithilfe von Drugs.com und Stockley's in der in Publikation 2 (Kap. 4.2.) beschriebenen Analyse detektiert werden. Insgesamt waren 198 verschiedene Wirkstoffe an pDFIs beteiligt, davon 34 an schweren pDFIs. Von der pDFI bestehend aus Ibuprofen und Alkohol waren bis zu 16,7% der Patienten betroffen. Von den 20 Medikamenten, die am häufigsten von Patienten eingenommen wurden, bestand bei 15 der Präparate die Gefahr einer pDFI. Dabei muss jedoch beachtet werden, dass die Wahrscheinlichkeit, dass ein Patient von einer dieser möglichen Interaktionen tatsächlich klinisch betroffen war, eher gering ist, da viele dieser pDFIs auf bestimmten Nahrungs- und Genussmitteln basieren, deren Konsum in der Studie nicht erfasst wurde. Viele pDFIs sind bspw. Interaktionen mit Alkohol oder Tabak, die einen gegebenenfalls regelmäßigen Alkohol- bzw. Tabakgebrauch voraussetzen. Auch die teilweise sehr relevanten CYP-Interaktionen mit Grapefruitsaft treten klinisch eher selten auf [136], sollten aber trotzdem nicht vernachlässigt werden [137, 138].

Verschiedene, möglicherweise limitierende Faktoren dieser Arbeit sollten beachtet werden. Zum einen basierten die Analysen der vorliegenden Dissertation auf Querschnittsdaten. Zum anderen beruhte die Definition von Rx-Medikamenten auf in

Deutschland zum Zeitpunkt der Datenanalyse verschreibungspflichtigen Medikamenten, die gegebenenfalls zu einem anderen Zeitpunkt nicht mehr für den jeweiligen Zweck zugelassen oder in anderen Ländern möglicherweise nicht verschreibungspflichtig und daher frei erhältlich sind. Durch sorgfältige Datenerhebung und detaillierte Erfassung von Patientendaten mithilfe von Anamnese, Interviews und Patientenakten wurde versucht, Unvollständigkeiten der Angaben so minimal wie möglich zu halten. Jedoch werden Studien zufolge besonders OTC und eigenständig eingenommene Präparate aus Drogerien oder Reformhäusern regelmäßig von Patienten vergessen anzugeben [139, 140]. Eine Erfassung der tatsächlichen Einnahme und Applikation der Medikamente erfolgte nicht, sodass die tatsächliche Adhärenz nicht eingeschätzt werden kann. Weiterhin ist es unklar, ob Patienten Empfehlungen und Vorgaben ihrer behandelnden Ärzte zur Vermeidung von pDDIs wie die Einhaltung zeitlicher Abstände zwischen Mahlzeiten oder der Applikation verschiedener Medikamente berücksichtigten. Die Therapieadhärenz ist generell ein entscheidender Faktor für das Auftreten von DDIs, da vor allem durch falsche Dosierungen oder nicht sachgemäße Einnahme der Medikamente DDIs auftreten können [141, 142]. Da viele pDDIs von individuellen Faktoren wie dem Metabolismus des Patienten abhängig sind [143–145], bezieht sich diese Arbeit auf *potenzielle* Medikamenteninteraktionen. Ob und wie diese in der Realität bei Patienten zu unerwünschten Arzneimittelwirkungen führen, wurde in der vorliegenden Arbeit nicht untersucht, genauso wenig, ob behandelnde Ärzte eventuell über die pDDIs ihrer Patienten informiert waren und diese gegebenenfalls nach einer Risiko-/Nutzenbewertung in Kauf nahmen. Möglicherweise wurden bestimmte pDDIs auch gezielt für erwünschte Wechselwirkungen genutzt, jedoch wurde dies nicht für diese Arbeit erfasst.

Um die klinischen Konsequenzen von pDDIs bei Patienten mit MS zu untersuchen, sollten zusätzlich in zukünftigen Studien longitudinale Untersuchungen auf auftretende DDIs bei Patienten durchgeführt werden. Auch denkbar wären bspw. Patientenbefragungen, mithilfe derer eingeschätzt werden kann, ob Patienten über die Problematik von PP und pDDIs aufgeklärt sind. In diesem Zusammenhang sollte weiterhin erfasst werden, ob Patienten wissen, worauf sie achten sollten, bspw. in Bezug auf Nahrungs- und Genussmittel oder die zeitliche Abfolge der Medikamenteneinnahme, aber auch hinsichtlich eventuell auftretender früher Anzeichen für DDIs. Für solche Fälle sollten konkrete Handlungsanweisungen für die Patienten vorliegen, sowie ein direkter Ansprechpartner bekannt sein. Das kann bspw. der Hausarzt sein, an den sich Patienten

bei Fragen oder Problemen bezüglich ihrer Medikation wenden können. Der Allgemeinmediziner als Bezugsperson kann einen Überblick über den Medikationsplan der Patienten im Ganzen haben und diesen modifizieren sowie bei spezifischen Fragen an die spezialisierte Fachrichtung weitervermitteln. Auf Seiten des medizinischen Fachpersonal sollten zukünftige Studien erfassen, inwiefern Ärzte und Apotheker sich der Problematik bewusst sind und wie sie damit umgehen.

Ein weiterer Ansatz zur Vermeidung bzw. Verminderung von DDIs wäre das therapeutische *drug monitoring* (Medikamentenspiegelbestimmung), mit dessen Hilfe die Plasmakonzentration von Wirkstoffen bestimmt werden kann, sodass zu hohe oder zu niedrige Plasmaspiegel erkannt und optimal eingestellt werden können. Bezüglich CDSS/DDIDs besteht großes Potential, um in Zukunft die Detektion von pDDIs weiter zu verbessern. Beispielsweise könnten vermehrt auch Kombinationen aus mehr als zwei Medikamenten hinsichtlich pDDIs betrachtet werden [146]. Es wäre außerdem denkbar, zukünftig *deep-learning* Verfahren einzusetzen, um pDDIs bereits anhand ihrer Wirkstoffstruktur vorauszusagen oder automatisch aus wissenschaftlichen Arbeiten zu extrahieren [147, 148]. Die Weiterentwicklung und bessere Integration von DDIDs bzw. CDSS in klinische Informationssysteme könnte künftig helfen, zeit- und kostensparend eine sichere und individualisierte medikamentöse Patientenversorgung zu unterstützen. Dies zeigt die Notwendigkeit und Relevanz dieser Arbeit für die Zukunft der Therapie von Patienten von MS. Die Neuartigkeit der hier gewonnenen Erkenntnisse verdeutlicht die bisherige Forschungslücke und es konnten Ansätze für weitere Forschungen zum Thema Interaktionssoftwares, pDDIs und PP bei Patienten mit MS geschaffen werden.

6. Zusammenfassung

Die Multiple Sklerose (MS) ist eine immunmedierte, chronisch neurologische Erkrankung, die aufgrund der individuell heterogenen Symptomatik sehr unterschiedliche Folgen für die betroffenen Patienten haben kann. Dementsprechend kommen neben den DMDs eine Vielfalt von symptomatischen Therapien sowie Medikamenten für die Behandlung eventueller Komorbiditäten zum Einsatz, was in Polypharmazie (PP) resultieren kann. PP, also die simultane Einnahme von \geq fünf Medikamenten (totale PP) bzw. von \geq fünf verschreibungspflichtigen Medikamenten (Rx-PP), stellt bspw. durch eine verringerte Therapieadhärenz einen Risikofaktor für negative Auswirkungen auf den Therapieerfolg dar. Neben PP sind auch potenzielle Medikamenteninteraktionen (*potential drug-drug interactions*, pDDIs) sowie potenzielle Medikamenten-Nahrungsmittelinteraktionen (pDFIs, *potential drug-food interactions*) im komplexen Therapiemanagement von Patienten mit MS zu beachten. In der Vergangenheit wurden jedoch kaum Forschungsergebnisse zu PP und pDDIs bei Patienten mit MS publiziert. Vor allem ein Vergleich verschiedener Interaktionssoftwares auf diesem Gebiet stellt eine Forschungslücke dar, die die vorliegende Dissertation zu schließen versucht. Daher war es Gegenstand dieser Arbeit, die Prävalenz sowie Schwere von pDDIs bei Patienten mit MS einzuschätzen und verschiedene, dafür verwendete Interaktionssoftwares zu vergleichen. Mithilfe der drei Interaktionssoftwares MediQ, Stockley's und Drugs.com wurden in der vorliegenden Arbeit die Medikationsdaten von 627 Patienten mit MS bzw. klinisch isoliertem Syndrom (*clinically isolated syndrome*, CIS) auf pDDIs analysiert. Weiterhin wurde die Assoziation zwischen PP und pDDIs untersucht. Risikofaktoren für schwere pDDIs wurden ebenfalls identifiziert und pDFIs erhoben.

Durchschnittlich verwendete jeder Patient mit MS 5,3 Medikamente. Die PP-Rate betrug 53,3% (totale PP) bzw. 38,6% (Rx-PP). Das Auftreten von PP jeglicher Form war signifikant assoziiert mit dem Auftreten mindestens einer pDDI, wovon 70,3% der Patienten betroffen waren. Die durchschnittliche Anzahl an pDDIs p. P. unterschied sich je nach verwendeter Interaktionssoftware. Unter Verwendung der Kombination von MediQ und Stockley's wurden im Durchschnitt 4,6 pDDIs p. P. identifiziert, mithilfe von Drugs.com sowie Stockley's waren es 4,1 pDDIs. Mithilfe aller drei Interaktionssoftwares waren es 5,7 pDDIs, darunter 0,9 schwere pDDIs je Patient. Die Einschätzung der Schweregrade war stark abhängig von der verwendeten Software. Die Ergebnisse der drei Softwares variierten inhaltlich sehr stark. Nur 18,9% der detektierten pDDIs waren in allen drei Datenbanken

enthalten, wovon wiederum nur 17,3% konsistent mit dem gleichen Schweregrad eingestuft wurden. Jede Software ergab pDDIs, die in den anderen beiden nicht aufgelistet waren. Risikofaktoren für das Auftreten mindestens einer schweren pDDI waren u. a. eine erhöhte Anzahl eingenommener Medikamente, ein höheres Alter und ein niedrigeres Bildungsniveau. Von den detektierten pDDIs resultierten etwa 20% aus der Verwendung von verschreibungsfreien Medikamenten. Es waren 198 der von den MS-Patienten verwendeten Wirkstoffe an pDFIs beteiligt.

Aus den Ergebnissen der vorliegenden Arbeit kann abgeleitet werden, dass sowohl PP als auch pDDIs in der Therapie der MS von hoher Relevanz sind. Dies könnte eine Basis für zukünftige Studien darstellen, um die Medikamentensicherheit von MS-Patienten weiter zu evaluieren und zu verbessern. Longitudinalstudien könnten helfen, die nicht nur pharmakologisch möglichen, sondern klinisch tatsächlich auftretenden DDIs in Form von unzureichenden Therapieeffekten oder Intoxikationen zu erfassen. Durch ein stärkeres Bewusstsein für die Themen PP, pDDIs und pDFIs sowohl auf Seiten von medizinischem Fachpersonal als auch auf Seiten der Patienten sowie eine Optimierung des Therapiemanagements könnte in Zukunft unangemessene (Rx-) PP reduziert und das Vorliegen von pDDIs bzw. pDFIs vermieden werden. Ärzte und Apotheker können aktuell durch die Verwendung von mehr als einer Interaktionssoftware eine bessere Übersicht über pDDIs sowie pDFIs ihrer Patienten erlangen.

7. Literaturverzeichnis

- [1] Filippi M, Bar-Or A, Piehl F, et al. Multiple sclerosis. *Nat Rev Dis Primers* 2018; 4: 43. doi:10.1038/s41572-018-0041-4
- [2] Lassmann H. Multiple Sclerosis Pathology. *Cold Spring Harb Perspect Med* 2018; 8: a028936. doi:10.1101/cshperspect.a028936
- [3] Goodin DS. The epidemiology of multiple sclerosis: insights to a causal cascade. *Handb Clin Neurol* 2016; 138: 173–206. doi:10.1016/B978-0-12-802973-2.00011-2
- [4] Walton C, King R, Rechtman L, et al. Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition. *Mult Scler* 2020; 26: 1816–1821. doi:10.1177/1352458520970841
- [5] Wallin MT, Culpepper WJ, Campbell JD, et al. The prevalence of MS in the United States: A population-based estimate using health claims data. *Neurology* 2019; 92: e1029–e1040. doi:10.1212/WNL.0000000000007035
- [6] Kingwell E, Marriott JJ, Jetté N, et al. Incidence and prevalence of multiple sclerosis in Europe: a systematic review. *BMC Neurol* 2013; 13: 128. doi:10.1186/1471-2377-13-128
- [7] Garg N, Smith TW. An update on immunopathogenesis, diagnosis, and treatment of multiple sclerosis. *Brain Behav* 2015; 5: e00362. doi:10.1002/brb3.362
- [8] Cramer SP, Modvig S, Simonsen HJ, et al. Permeability of the blood-brain barrier predicts conversion from optic neuritis to multiple sclerosis. *Brain* 2015; 138: 2571–2583. doi:10.1093/brain/awv203
- [9] Hunter SF. Overview and diagnosis of multiple sclerosis. *Am J Manag Care* 2016; 22: s141-150
- [10] Olsson T, Barcellos LF, Alfredsson L. Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. *Nat Rev Neurol* 2017; 13: 25–36. doi:10.1038/nrneurol.2016.187
- [11] Waubant E, Lucas R, Mowry E, et al. Environmental and genetic risk factors for MS: an integrated review. *Ann Clin Transl Neurol* 2019; 6: 1905–1922. doi:10.1002/acn3.50862
- [12] Bhigjee AI, Moodley K, Ramkisson K. Multiple sclerosis in KwaZulu Natal, South Africa: an epidemiological and clinical study. *Mult Scler* 2007; 13: 1095–1099. doi:10.1177/1352458507079274
- [13] Golden LC, Voskuhl R. The importance of studying sex differences in disease: The example of multiple sclerosis. *J Neurosci Res* 2017; 95: 633–643. doi:10.1002/jnr.23955
- [14] Moutsianas L, Jostins L, Beecham AH, et al. Class II HLA interactions modulate genetic risk for multiple sclerosis. *Nat Genet* 2015; 47: 1107–1113. doi:10.1038/ng.3395
- [15] Ghareghani M, Reiter RJ, Zibara K, et al. Latitude, Vitamin D, Melatonin, and Gut Microbiota Act in Concert to Initiate Multiple Sclerosis: A New Mechanistic Pathway. *Front Immunol* 2018; 9: 2484. doi:10.3389/fimmu.2018.02484
- [16] Degelman ML, Herman KM. Smoking and multiple sclerosis: A systematic review and meta-analysis using the Bradford Hill criteria for causation. *Mult Scler Relat Disord*

- 2017; 17: 207–216. doi:10.1016/j.msard.2017.07.020
- [17] Rommer PS, Eichstädt K, Ellenberger D, et al. Symptomatology and symptomatic treatment in multiple sclerosis: Results from a nationwide MS registry. *Mult Scler* 2019; 25: 1641–1652. doi:10.1177/1352458518799580
- [18] Travers BS, Tsang BK-T, Barton JL. Multiple sclerosis: Diagnosis, disease-modifying therapy and prognosis. *Aust J Gen Pract* 2022; 51: 199–206. doi:10.31128/AJGP-07-21-6103
- [19] Toledano M, Weinshenker BG, Solomon AJ. A Clinical Approach to the Differential Diagnosis of Multiple Sclerosis. *Curr Neurol Neurosci Rep* 2015; 15: 57. doi:10.1007/s11910-015-0576-7
- [20] Solomon AJ. Diagnosis, Differential Diagnosis, and Misdiagnosis of Multiple Sclerosis. *Continuum (Minneap Minn)* 2019; 25: 611–635. doi:10.1212/CON.0000000000000728
- [21] Sparaco M, Lavorgna L, Bonavita S. Psychiatric disorders in multiple sclerosis. *J Neurol* 2021; 268: 45–60. doi:10.1007/s00415-019-09426-6
- [22] Crayton HJ, Rossman HS. Managing the symptoms of multiple sclerosis: A multimodal approach. *Clinical Therapeutics* 2006; 28: 445–460. doi:10.1016/j.clinthera.2006.04.005
- [23] Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983; 33: 1444–1452. doi:10.1212/wnl.33.11.1444
- [24] Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018; 17: 162–173. doi:10.1016/S1474-4422(17)30470-2
- [25] Hemond CC, Bakshi R. Magnetic Resonance Imaging in Multiple Sclerosis. *Cold Spring Harb Perspect Med* 2018; 8: a028969. doi:10.1101/cshperspect.a028969
- [26] Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology* 2014; 83: 278–286. doi:10.1212/WNL.0000000000000560
- [27] Miller DH, Chard DT, Ciccarelli O. Clinically isolated syndromes. *The Lancet Neurology* 2012; 11: 157–169. doi:10.1016/S1474-4422(11)70274-5
- [28] Confavreux C, Vukusic S. The clinical course of multiple sclerosis. *Handb Clin Neurol* 2014; 122: 343–369. doi:10.1016/B978-0-444-52001-2.00014-5
- [29] Hemmer B. Diagnose und Therapie der Multiplen Sklerose, Neuromyelitis-optica-Spektrum- Erkrankungen und MOG-IgG-assoziierten Erkrankungen, Sk2-Leitlinie. 2021; Im Internet: https://dgn.org/wp-content/uploads/2021/04/030050_LL-Report_Multiple_Sklerose_2021.pdf; Stand: 09.04.2022
- [30] Wiendl H, Gold R, Berger T, et al. [Multiple sclerosis treatment consensus group (MSTCG): position paper on disease-modifying treatment of multiple sclerosis 2021 (white paper)]. *Nervenarzt* 2021; 92: 773–801. doi:10.1007/s00115-021-01157-2
- [31] Hauser SL, Cree BAC. Treatment of Multiple Sclerosis: A Review. *The American Journal of Medicine* 2020; 133: 1380-1390.e2. doi:10.1016/j.amjmed.2020.05.049
- [32] Lamb YN. Ocrelizumab: A Review in Multiple Sclerosis. *Drugs* 2022; 82: 323–334. doi:10.1007/s40265-022-01672-9

- [33] Rommer PS, Sühnel A, König N, et al. Coping with multiple sclerosis-the role of social support. *Acta Neurol Scand* 2017; 136: 11–16. doi:10.1111/ane.12673
- [34] McGinley MP, Goldschmidt CH, Rae-Grant AD. Diagnosis and Treatment of Multiple Sclerosis: A Review. *JAMA* 2021; 325: 765–779. doi:10.1001/jama.2020.26858
- [35] Masnoon N, Shakib S, Kalisch-Ellett L, et al. What is polypharmacy? A systematic review of definitions. *BMC Geriatr* 2017; 17: 230. doi:10.1186/s12877-017-0621-2
- [36] Zhang N, Sundquist J, Sundquist K, et al. An Increasing Trend in the Prevalence of Polypharmacy in Sweden: A Nationwide Register-Based Study. *Front Pharmacol* 2020; 11: 326. doi:10.3389/fphar.2020.00326
- [37] Moßhammer D, Haumann H, Mörike K, et al. Polypharmacy-an Upward Trend with Unpredictable Effects. *Dtsch Arztebl Int* 2016; 113: 627–633. doi:10.3238/arztebl.2016.0627
- [38] Guthrie B, Makubate B, Hernandez-Santiago V, et al. The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995–2010. *BMC Medicine* 2015; 13: 74. doi:10.1186/s12916-015-0322-7
- [39] Marcum ZA, Gellad WF. Medication adherence to multidrug regimens. *Clin Geriatr Med* 2012; 28: 287–300. doi:10.1016/j.cger.2012.01.008
- [40] Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. *Expert Opin Drug Saf* 2014; 13: 57–65. doi:10.1517/14740338.2013.827660
- [41] Knopf H, Grams D. [Medication use of adults in Germany: results of the German Health Interview and Examination Survey for Adults (DEGS1)]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2013; 56: 868–877. doi:10.1007/s00103-013-1667-8
- [42] Hines LE, Murphy JE. Potentially Harmful Drug–Drug Interactions in the Elderly: A Review. *The American Journal of Geriatric Pharmacotherapy* 2011; 9: 364–377. doi:10.1016/j.amjopharm.2011.10.004
- [43] Meibohm B, Derendorf H. Basic concepts of pharmacokinetic/pharmacodynamic (PK/PD) modelling. *Int J Clin Pharmacol Ther* 1997; 35: 401–413
- [44] Bahar MA, Setiawan D, Hak E, et al. Pharmacogenetics of drug-drug interaction and drug-drug-gene interaction: a systematic review on CYP2C9, CYP2C19 and CYP2D6. *Pharmacogenomics* 2017; 18: 701–739. doi:10.2217/pgs-2017-0194
- [45] Prybys KM. Deadly drug interactions in emergency medicine. *Emerg Med Clin North Am* 2004; 22: 845–863. doi:10.1016/j.emc.2004.05.001
- [46] Tsifi A, Papaxoinis G, Diamantopoulos P, et al. A life-threatening drug-drug interaction between capecitabine and brivudine in a patient with metastatic breast cancer. *J Chemother* 2019; 31: 424–427. doi:10.1080/1120009X.2019.1665875
- [47] Zhang C, Shen L, Cui M, et al. Ticagrelor-induced life-threatening bleeding via the cyclosporine-mediated drug interaction: A case report. *Medicine (Baltimore)* 2017; 96: e8065. doi:10.1097/MD.0000000000008065
- [48] Hougaard Christensen MM, Bruun Haastrup M, Øhlenschlaeger T, et al. Interaction potential between clarithromycin and individual statins-A systematic review. *Basic Clin Pharmacol Toxicol* 2020; 126: 307–317. doi:10.1111/bcpt.13343

- [49] Moura CS, Acurcio FA, Belo NO. Drug-drug interactions associated with length of stay and cost of hospitalization. *J Pharm Pharm Sci* 2009; 12: 266–272. doi:10.18433/j35c7z
- [50] Rekić D, Reynolds KS, Zhao P, et al. Clinical Drug-Drug Interaction Evaluations to Inform Drug Use and Enable Drug Access. *J Pharm Sci* 2017; 106: 2214–2218. doi:10.1016/j.xphs.2017.04.016
- [51] Dechanont S, Maphanta S, Butthum B, et al. Hospital admissions/visits associated with drug-drug interactions: a systematic review and meta-analysis. *Pharmacoepidemiol Drug Saf* 2014; 23: 489–497. doi:10.1002/pds.3592
- [52] Ernst FR, Grizzle AJ. Drug-related morbidity and mortality: updating the cost-of-illness model. *J Am Pharm Assoc (Wash)* 2001; 41: 192–199. doi:10.1016/s1086-5802(16)31229-3
- [53] Sultana J, Cutroneo P, Trifirò G. Clinical and economic burden of adverse drug reactions. *J Pharmacol Pharmacother* 2013; 4: S73-77. doi:10.4103/0976-500X.120957
- [54] Batta A, Kalra BS, Khirasaria R. Trends in FDA drug approvals over last 2 decades: An observational study. *Journal of Family Medicine and Primary Care* 2020; 9: 105–114. doi:10.4103/jfmpc.jfmpc_578_19
- [55] Roblek T, Vaupotic T, Mrhar A, et al. Drug-drug interaction software in clinical practice: a systematic review. *Eur J Clin Pharmacol* 2015; 71: 131–142. doi:10.1007/s00228-014-1786-7
- [56] Amkreutz J, Koch A, Buendgens L, et al. Clinical decision support systems differ in their ability to identify clinically relevant drug interactions of immunosuppressants in kidney transplant patients. *J Clin Pharm Ther* 2017; 42: 276–285. doi:10.1111/jcpt.12508
- [57] Kheshti R, Aalipour M, Namazi S. A comparison of five common drug-drug interaction software programs regarding accuracy and comprehensiveness. *J Res Pharm Pract* 2016; 5: 257–263. doi:10.4103/2279-042X.192461
- [58] Weingart SN, Toth M, Sands DZ, et al. Physicians' decisions to override computerized drug alerts in primary care. *Arch Intern Med* 2003; 163: 2625–2631. doi:10.1001/archinte.163.21.2625
- [59] Skierlo S, Rommer PS, Zettl UK. Symptomatic treatment in multiple sclerosis-interim analysis of a nationwide registry. *Acta Neurol Scand* 2017; 135: 394–399. doi:10.1111/ane.12612
- [60] Toosy A, Ciccarelli O, Thompson A. Symptomatic treatment and management of multiple sclerosis. *Handb Clin Neurol* 2014; 122: 513–562. doi:10.1016/B978-0-444-52001-2.00023-6
- [61] Flachenecker P, Eichstädt K, Berger K, et al. [Multiple sclerosis in Germany: updated analysis of the German MS Registry 2014-2018]. *Fortschr Neurol Psychiatr* 2020; 88: 436–450. doi:10.1055/a-0985-4124
- [62] Murray CJ, Acharya AK. Understanding DALYs (disability-adjusted life years). *J Health Econ* 1997; 16: 703–730. doi:10.1016/s0167-6296(97)00004-0
- [63] Simon DK, Tanner CM, Brundin P. Parkinson Disease Epidemiology, Pathology, Genetics, and Pathophysiology. *Clin Geriatr Med* 2020; 36: 1–12. doi:10.1016/j.cger.2019.08.002

- [64] Soria Lopez JA, González HM, Léger GC. Alzheimer's disease. *Handb Clin Neurol* 2019; 167: 231–255. doi:10.1016/B978-0-12-804766-8.00013-3
- [65] Schenker Y, Park SY, Jeong K, et al. Associations Between Polypharmacy, Symptom Burden, and Quality of Life in Patients with Advanced, Life-Limiting Illness. *J Gen Intern Med* 2019; 34: 559–566. doi:10.1007/s11606-019-04837-7
- [66] Machón M, Larrañaga I, Dorronsoro M, et al. Health-related quality of life and associated factors in functionally independent older people. *BMC Geriatr* 2017; 17: 19. doi:10.1186/s12877-016-0410-3
- [67] Frahm N, Hecker M, Langhorst SE, et al. The risk of polypharmacy, comorbidities and drug–drug interactions in women of childbearing age with multiple sclerosis. *Ther Adv Neurol Disord* 2020; 13: 1756286420969501. doi:10.1177/1756286420969501
- [68] Preston CL. *Stockley's drug interactions*. 12. Aufl. London: Pharmaceutical Press; 2020
- [69] Bachmann P, Frahm N, Debus JL, et al. Prevalence and Severity of Potential Drug-Drug Interactions in Patients with Multiple Sclerosis with and without Polypharmacy. *Pharmaceutics* 2022; 14: 592. doi:10.3390/pharmaceutics14030592
- [70] Debus JL, Bachmann P, Frahm N, et al. Associated factors of potential drug-drug interactions and drug-food interactions in patients with multiple sclerosis. *Ther Adv Chronic Dis* 2022; 13: 20406223221108390. doi:10.1177/20406223221108391
- [71] Hecker M, Frahm N, Bachmann P, et al. Screening for severe drug-drug interactions in patients with multiple sclerosis: A comparison of three drug interaction databases. *Front Pharmacol* 2022; 13: 946351. doi:10.3389/fphar.2022.946351
- [72] Shannon P, Markiel A, Ozier O, et al. Cytoscape: a software environment for integrated models of biomolecular interaction networks. *Genome Res* 2003; 13: 2498–2504. doi:10.1101/gr.1239303
- [73] Kontis V, Bennett JE, Mathers CD, et al. Future life expectancy in 35 industrialised countries: projections with a Bayesian model ensemble. *The Lancet* 2017; 389: 1323–1335. doi:10.1016/S0140-6736(16)32381-9
- [74] Lancet T. Making more of multimorbidity: an emerging priority. *The Lancet* 2018; 391: 1637. doi:10.1016/S0140-6736(18)30941-3
- [75] Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; 386: 743–800. doi:10.1016/S0140-6736(15)60692-4
- [76] Davidson HE. The Many Faces of Polypharmacy. *Consult Pharm* 2018; 33: 286. doi:10.4140/TCP.n.2018.286
- [77] Wastesson JW, Morin L, Tan ECK, et al. An update on the clinical consequences of polypharmacy in older adults: a narrative review. *Expert Opin Drug Saf* 2018; 17: 1185–1196. doi:10.1080/14740338.2018.1546841
- [78] Cascorbi I. Drug Interactions—Principles, Examples and Clinical Consequences. *Dtsch Arztebl Int* 2012; 109: 546–556. doi:10.3238/arztebl.2012.0546
- [79] Thelen J, Zvonarev V, Lam S, et al. Polypharmacy in Multiple Sclerosis: Current

- Knowledge and Future Directions. *Mo Med* 2021; 118: 239–245
- [80] Thelen JM, Lynch SG, Bruce AS, et al. Polypharmacy in multiple sclerosis: relationship with fatigue, perceived cognition, and objective cognitive performance. *J Psychosom Res* 2014; 76: 400–404. doi:10.1016/j.jpsychores.2014.02.013
- [81] Jelinek GA, Weiland TJ, Hadgkiss EJ, et al. Medication use in a large international sample of people with multiple sclerosis: associations with quality of life, relapse rate and disability. *Neurol Res* 2015; 37: 662–673. doi:10.1179/1743132815Y.0000000036
- [82] Evans C, Marrie RA, Zhu F, et al. Adherence to disease-modifying therapies for multiple sclerosis and subsequent hospitalizations. *Pharmacoepidemiol Drug Saf* 2017; 26: 702–711. doi:10.1002/pds.4207
- [83] Frahm N, Hecker M, Zettl UK. Multi-drug use among patients with multiple sclerosis: A cross-sectional study of associations to clinicodemographic factors. *Sci Rep* 2019; 9: 3743. doi:10.1038/s41598-019-40283-5
- [84] Frahm N, Hecker M, Zettl UK. Polypharmacy in patients with multiple sclerosis: a gender-specific analysis. *Biol Sex Differ* 2019; 10: 27. doi:10.1186/s13293-019-0243-9
- [85] Frahm N, Hecker M, Zettl UK. Polypharmacy in outpatients with relapsing-remitting multiple sclerosis: A single-center study. *PLoS One* 2019; 14: e0211120. doi:10.1371/journal.pone.0211120
- [86] Zanghì A, D’Amico E, Lo Fermo S, et al. Exploring polypharmacy phenomenon in newly diagnosed relapsing-remitting multiple sclerosis: a cohort ambispective single-centre study. *Ther Adv Chronic Dis* 2021; 12: 2040622320983121. doi:10.1177/2040622320983121
- [87] Myers LW, Phillips JT. Polypharmacy in multiple sclerosis. *Epilepsy Res Suppl* 1996; 11: 181–195
- [88] Beiske GAG, Holmøy T, Beiske AG, et al. Antiepileptic and Antidepressive Polypharmacy in Patients with Multiple Sclerosis. *Mult Scler Int* 2015; 2015: 317859. doi:10.1155/2015/317859
- [89] Maust DT, Strominger J, Kim HM, et al. Prevalence of Central Nervous System-Active Polypharmacy Among Older Adults With Dementia in the US. *JAMA* 2021; 325: 952–961. doi:10.1001/jama.2021.1195
- [90] Giovannini S, Laudisio A, Navarini L, et al. Polypharmacy is a determinant of hospitalization in Parkinson’s disease. *Eur Rev Med Pharmacol Sci* 2021; 25: 4810–4817. doi:10.26355/eurrev_202107_26394
- [91] Müller-Rebstein S, Trenkwalder C, Ebentheuer J, et al. Drug Safety Analysis in a Real-Life Cohort of Parkinson’s Disease Patients with Polypharmacy. *CNS Drugs* 2017; 31: 1093–1102. doi:10.1007/s40263-017-0478-0
- [92] Pflugbeil S, Böckl K, Pongratz R, et al. Drug interactions in the treatment of rheumatoid arthritis and psoriatic arthritis. *Rheumatol Int* 2020; 40: 511–521. doi:10.1007/s00296-020-04526-3
- [93] Trenaman SC, Bowles SK, Kirkland S, et al. An examination of three prescribing cascades in a cohort of older adults with dementia. *BMC Geriatr* 2021; 21: 297. doi:10.1186/s12877-021-02246-2

- [94] Bivol S, Mellick GD, Gratten J, et al. Australian Parkinson's Genetics Study (APGS): pilot (n=1532). *BMJ Open* 2022; 12: e052032. doi:10.1136/bmjopen-2021-052032
- [95] Weih M, Roßnagel F, Dikow H, et al. [Data on multiple sclerosis in Germany and their representation in the ambulatory registry NeuroTransData (NTD) network]. *Fortschr Neurol Psychiatr* 2020; 88: 379–385. doi:10.1055/a-1130-6222
- [96] Laugisch O, Holtfreter B, Pink C, et al. Polypharmacy and saliva volumes in the northeast of Germany – The Study of Health in Pomerania. *Community Dentistry and Oral Epidemiology* 2022; 50: 139–146. doi:10.1111/cdoe.12644
- [97] Nind J, Smith A, Devananda M, et al. A whole of population retrospective observational study on the rates of polypharmacy in New Zealand 2014 to 2018 Polypharmacy in New Zealand: What is the current status? *Health Sci Rep* 2021; 4: e263. doi:10.1002/hsr2.263
- [98] Kornholt J, Christensen MB. Prevalence of polypharmacy in Denmark. *Dan Med J* 2020; 67: A12190680
- [99] Mielke N, Huscher D, Douros A, et al. Self-reported medication in community-dwelling older adults in Germany: results from the Berlin Initiative Study. *BMC Geriatrics* 2020; 20: 22. doi:10.1186/s12877-020-1430-6
- [100] Pazan F, Wehling M. Polypharmacy in older adults: a narrative review of definitions, epidemiology and consequences. *Eur Geriatr Med* 2021; 12: 443–452. doi:10.1007/s41999-021-00479-3
- [101] Zorina OI, Haueis P, Semmler A, et al. Comparative evaluation of the drug interaction screening programs MediQ and ID PHARMA CHECK in neurological inpatients. *Pharmacoepidemiol Drug Saf* 2012; 21: 872–880. doi:10.1002/pds.3279
- [102] Zorina OI, Haueis P, Greil W, et al. Comparative performance of two drug interaction screening programmes analysing a cross-sectional prescription dataset of 84,625 psychiatric inpatients. *Drug Saf* 2013; 36: 247–258. doi:10.1007/s40264-013-0027-9
- [103] Shariff A, Belagodu Sridhar S, Abdullah Basha NF, et al. Assessing Consistency of Drug-Drug Interaction-Related Information Across Various Drug Information Resources. *Cureus* 2021; 13: e13766. doi:10.7759/cureus.13766
- [104] Vanham D, Spinewine A, Hantson P, et al. Drug-drug interactions in the intensive care unit: Do they really matter? *J Crit Care* 2017; 38: 97–103. doi:10.1016/j.jcrc.2016.09.014
- [105] Sancar M, Kaşık A, Okuyan B, et al. Determination of Potential Drug-Drug Interactions Using Various Software Programs in a Community Pharmacy Setting. *Turk J Pharm Sci* 2019; 16: 14–19. doi:10.4274/tjps.30932
- [106] Fung KW, Kapusnik-Uner J, Cunningham J, et al. Comparison of three commercial knowledge bases for detection of drug-drug interactions in clinical decision support. *J Am Med Inform Assoc* 2017; 24: 806–812. doi:10.1093/jamia/ocx010
- [107] Abarca J, Malone DC, Armstrong EP, et al. Concordance of severity ratings provided in four drug interaction compendia. *J Am Pharm Assoc (2003)* 2004; 44: 136–141. doi:10.1331/154434504773062582
- [108] Suriyapakorn B, Chairat P, Boonyoprakarn S, et al. Comparison of potential drug-drug interactions with metabolic syndrome medications detected by two databases. *PLoS*

- One 2019; 14: e0225239. doi:10.1371/journal.pone.0225239
- [109] Hines LE, Malone DC, Murphy JE. Recommendations for generating, evaluating, and implementing drug-drug interaction evidence. *Pharmacotherapy* 2012; 32: 304–313. doi:10.1002/j.1875-9114.2012.01024.x
- [110] Hammar T, Hamqvist S, Zetterholm M, et al. Current Knowledge about Providing Drug–Drug Interaction Services for Patients—A Scoping Review. *Pharmacy (Basel)* 2021; 9: 69. doi:10.3390/pharmacy9020069
- [111] Kusch MK, Haefeli WE, Seidling HM. How to meet patients’ individual needs for drug information - a scoping review. *Patient Prefer Adherence* 2018; 12: 2339–2355. doi:10.2147/PPA.S173651
- [112] Wang LM, Wong M, Lightwood JM, et al. Black box warning contraindicated comedications: concordance among three major drug interaction screening programs. *Ann Pharmacother* 2010; 44: 28–34. doi:10.1345/aph.1M475
- [113] Prely H, Herledan C, Caffin AG, et al. Real-life drug-drug and herb-drug interactions in outpatients taking oral anticancer drugs: comparison with databases. *J Cancer Res Clin Oncol* 2021; doi:10.1007/s00432-021-03645-z
- [114] Merlo J, Liedholm H, Lindblad U, et al. Prescriptions with potential drug interactions dispensed at Swedish pharmacies in January 1999: cross sectional study. *BMJ* 2001; 323: 427–428
- [115] Balasubramanian R, Maideen NMP. HMG-CoA Reductase Inhibitors (Statins) and their Drug Interactions Involving CYP Enzymes, P-glycoprotein and OATP Transporters—An Overview. *Curr Drug Metab* 2021; 22: 328–341. doi:10.2174/1389200222666210114122729
- [116] Hirota T, Fujita Y, Ieiri I. An updated review of pharmacokinetic drug interactions and pharmacogenetics of statins. *Expert Opin Drug Metab Toxicol* 2020; 16: 809–822. doi:10.1080/17425255.2020.1801634
- [117] Thérroux P, Ouimet H, McCans J, et al. Aspirin, heparin, or both to treat acute unstable angina. *N Engl J Med* 1988; 319: 1105–1111. doi:10.1056/NEJM198810273191701
- [118] Eriksson BI, Rosencher N, Friedman RJ, et al. Concomitant use of medication with antiplatelet effects in patients receiving either rivaroxaban or enoxaparin after total hip or knee arthroplasty. *Thromb Res* 2012; 130: 147–151. doi:10.1016/j.thromres.2011.12.005
- [119] Vane JR, Botting RM. The mechanism of action of aspirin. *Thromb Res* 2003; 110: 255–258. doi:10.1016/s0049-3848(03)00379-7
- [120] Sangkuhl K, Klein TE, Altman RB. PharmGKB summary: citalopram pharmacokinetics pathway. *Pharmacogenet Genomics* 2011; 21: 769–772. doi:10.1097/FPC.0b013e328346063f
- [121] Pae C-U, Wang S-M, Lee S-J, et al. Antidepressant and QT interval prolongation, how should we look at this issue? Focus on citalopram. *Expert Opin Drug Saf* 2014; 13: 197–205. doi:10.1517/14740338.2013.840583
- [122] Roden DM. Predicting drug-induced QT prolongation and torsades de pointes. *J Physiol* 2016; 594: 2459–2468. doi:10.1113/JP270526

- [123] Bogetti-Salazar M, González-González C, Juárez-Cedillo T, et al. Severe potential drug-drug interactions in older adults with dementia and associated factors. *Clinics (Sao Paulo)* 2016; 71: 17–21. doi:10.6061/clinics/2016(01)04
- [124] Olesen C, Harbig P, Barat I, et al. Absence of „over-the-counter“ medicinal products in on-line prescription records: a risk factor of overlooking interactions in the elderly. *Pharmacoepidemiol Drug Saf* 2013; 22: 145–150. doi:10.1002/pds.3362
- [125] Dookeeram D, Bidaisee S, Paul JF, et al. Polypharmacy and potential drug-drug interactions in emergency department patients in the Caribbean. *Int J Clin Pharm* 2017; 39: 1119–1127. doi:10.1007/s11096-017-0520-9
- [126] Scherf-Clavel O. Drug-Drug Interactions With Over-The-Counter Medicines: Mind the Unprescribed. *Ther Drug Monit* 2022; 44: 253–274. doi:10.1097/FTD.0000000000000924
- [127] Gardiner P, Sadikova E, Filippelli AC, et al. Medical reconciliation of dietary supplements: don't ask, don't tell. *Patient Educ Couns* 2015; 98: 512–517. doi:10.1016/j.pec.2014.12.010
- [128] Floor-Schreudering A, Heringa M, Buurma H, et al. Missed drug therapy alerts as a consequence of incomplete electronic patient records in Dutch community pharmacies. *Ann Pharmacother* 2013; 47: 1272–1279. doi:10.1177/1060028013501992
- [129] Ramsdale E, Mohamed M, Yu V, et al. Polypharmacy, Potentially Inappropriate Medications, and Drug-Drug Interactions in Vulnerable Older Adults With Advanced Cancer Initiating Cancer Treatment. *Oncologist* 2022; 27: e580–e588. doi:10.1093/oncolo/oyac053
- [130] Hughes JE, Russo V, Walsh C, et al. Prevalence and Factors Associated with Potential Drug-Drug Interactions in Older Community-Dwelling Adults: A Prospective Cohort Study. *Drugs Aging* 2021; 38: 1025–1037. doi:10.1007/s40266-021-00898-8
- [131] Obreli Neto PR, Nobili A, de Lyra DP, et al. Incidence and predictors of adverse drug reactions caused by drug-drug interactions in elderly outpatients: a prospective cohort study. *J Pharm Pharm Sci* 2012; 15: 332–343. doi:10.18433/j3cc86
- [132] Jazbar J, Locatelli I, Horvat N, et al. Clinically relevant potential drug-drug interactions among outpatients: A nationwide database study. *Res Social Adm Pharm* 2018; 14: 572–580. doi:10.1016/j.sapharm.2017.07.004
- [133] Santos-Pérez MI, Fierro I, Salgueiro-Vázquez ME, et al. A polypharmacy risk prediction model for elderly patients based on sociodemographic and clinical factors. *Int J Clin Pharmacol Ther* 2018; 56: 577–584. doi:10.5414/CP203238
- [134] Morillo-Verdugo R, Sánchez-Rubio-Ferrández J, Gimeno-Gracia M, et al. Prevalence of polypharmacy and associated factors among patients living with HIV infection in Spain: The POINT study. *Enferm Infecc Microbiol Clin (Engl Ed)* 2022; 40: 7–13. doi:10.1016/j.eimce.2020.09.005
- [135] Frahm N, Hecker M, Zettl UK. Polypharmacy among patients with multiple sclerosis: a qualitative systematic review. *Expert Opin Drug Saf* 2020; 19: 139–145. doi:10.1080/14740338.2020.1720646
- [136] Reddy P, Ellington D, Zhu Y, et al. Serum concentrations and clinical effects of

- atorvastatin in patients taking grapefruit juice daily. *Br J Clin Pharmacol* 2011; 72: 434–441. doi:10.1111/j.1365-2125.2011.03996.x
- [137] Seden K, Dickinson L, Khoo S, et al. Grapefruit-drug interactions. *Drugs* 2010; 70: 2373–2407. doi:10.2165/11585250-000000000-00000
- [138] Zevin S, Benowitz NL. Drug interactions with tobacco smoking. An update. *Clin Pharmacokinet* 1999; 36: 425–438. doi:10.2165/00003088-199936060-00004
- [139] Tam VC, Knowles SR, Cornish PL, et al. Frequency, type and clinical importance of medication history errors at admission to hospital: a systematic review. *CMAJ* 2005; 173: 510–515. doi:10.1503/cmaj.045311
- [140] Abdolrasulnia M, Weichold N, Shewchuk R, et al. Agreement between medical record documentation and patient-reported use of nonsteroidal antiinflammatory drugs. *Am J Health Syst Pharm* 2006; 63: 744–747. doi:10.2146/ajhp050409
- [141] Salazar JA, Poon I, Nair M. Clinical consequences of polypharmacy in elderly: expect the unexpected, think the unthinkable. *Expert Opin Drug Saf* 2007; 6: 695–704. doi:10.1517/14740338.6.6.695
- [142] Cabri A, Barsegyan N, Postelnick M, et al. Pharmacist intervention on prescribing errors: Use of a standardized approach in the inpatient setting. *Am J Health Syst Pharm* 2021; 78: 2151–2158. doi:10.1093/ajhp/zxab278
- [143] Palleria C, Di Paolo A, Giofrè C, et al. Pharmacokinetic drug-drug interaction and their implication in clinical management. *J Res Med Sci* 2013; 18: 601–610
- [144] Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. *Pharmacol Ther* 2013; 138: 103–141. doi:10.1016/j.pharmthera.2012.12.007
- [145] Gonzaga de Andrade Santos TN, Mendonça da Cruz Macieira G, Cardoso Sodrè Alves BM, et al. Prevalence of clinically manifested drug interactions in hospitalized patients: A systematic review and meta-analysis. *PLoS One* 2020; 15: e0235353. doi:10.1371/journal.pone.0235353
- [146] Luong T-LT, McAnulty MJ, Evers DL, et al. Pre-clinical drug-drug interaction (DDI) of gefitinib or erlotinib with Cytochrome P450 (CYP) inhibiting drugs, fluoxetine and/or losartan. *Curr Res Toxicol* 2021; 2: 217–224. doi:10.1016/j.crttox.2021.05.006
- [147] Vo TH, Nguyen NTK, Kha QH, et al. On the road to explainable AI in drug-drug interactions prediction: A systematic review. *Comput Struct Biotechnol J* 2022; 20: 2112–2123. doi:10.1016/j.csbj.2022.04.021
- [148] Zhang T, Leng J, Liu Y. Deep learning for drug-drug interaction extraction from the literature: a review. *Brief Bioinform* 2020; 21: 1609–1627. doi:10.1093/bib/bbz087

8. Publikationen

8.1. Publikation 1

Prevalence and severity of potential drug-drug interactions in patients with multiple sclerosis with and without polypharmacy


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Article

Prevalence and Severity of Potential Drug–Drug Interactions in Patients with Multiple Sclerosis with and without Polypharmacy

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Abstract: Polypharmacy (PP) is a common problem in modern medicine, especially known to affect patients with chronic diseases such as multiple sclerosis (MS). With an increasing number of drugs taken, the risk of potential drug–drug interactions (pDDIs) is rising. This study aims to assess the prevalence and clinical relevance of polypharmacy and pDDIs in patients with MS. Pharmacological data of 627 patients with MS were entered into two drug–drug-interaction databases to determine the number and severity of pDDIs for each patient. The patients were divided into those with and without PP (total PP and prescription medication PP (Rx PP)). Of the 627 patients included, 53.3% and 38.6% had total PP and Rx PP, respectively. On average, every patient took 5.3 drugs. Of all patients, 63.8% had at least one pDDI with a mean of 4.6 pDDIs per patient. Less than 4% of all pDDIs were moderately severe or severe. Medication schedules should be checked for inappropriate medication and for possible interacting drugs to prevent pDDIs. Physicians as well as pharmacists should be more sensitive towards the relevance of pDDIs and know how they can be detected and avoided.

Keywords: multiple sclerosis; polypharmacy; drug–drug interactions; clinical decision support software; over-the-counter drugs; Rx drugs



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1. Introduction

Polypharmacy (PP) is the simultaneous use of multiple drugs and mostly defined as the intake of at least five drugs at the same time [1]. PP particularly affects elderly people with various illnesses and comorbidities and those with severe chronic diseases, such as patients with multiple sclerosis (MS) [2,3]. Within recent years, life expectancy has continued to rise and the prevalence of MS has increased [4]. Therefore, the significance of PP in elderly and patients with MS is also increasing. Globally, there are approximately 2.8 million patients diagnosed with MS [4], which is an immune-mediated disease affecting the central nervous system, causing demyelination, oligodendrocyte loss, synaptic and axon loss, as well as reactive gliosis [5]. As these processes are neither limited in time nor in location, symptoms of MS vary a lot [6] and the disease progression can hardly be predicted [7–9]. MS leads to an accumulation of disability, either with or without the occurrence of relapses. The disease course can be distinguished into three main subtypes [10]: the relapsing–remitting course (RRMS), the primary progressive course (PPMS) and the secondary progressive course (SPMS). An initial clinical episode with symptoms suggestive of MS is referred to as clinically isolated syndrome (CIS) [11].

There is still no cure for MS, but there are treatments that can alleviate the symptoms, prevent relapses and delay disease progression. Disease-modifying drugs (DMDs) for MS

are immunosuppressive or immunomodulatory [12–14]. While there are several DMDs available to treat patients with RRMS and SPMS [15,16], there is currently only one drug approved for patients with PPMS (ocrelizumab) [17]. Aside from DMDs, MS patients mostly require symptomatic drugs as well as medication for comorbidities. Patients with late-stage MS often suffer from multiple symptoms, such as gastrointestinal, psychiatric and motoric complaints [18]. The use of several symptomatic drugs in combination with DMDs and comorbidity therapeutics can quickly lead to PP in patients with MS [6,19]. Previous studies have shown that PP rates in MS patients range from 15% to 59% [2]. With an increasing number of drugs taken and with PP, the risk of potential drug–drug interactions (pDDIs) is increasing as well [19].

pDDIs are possible interactions between two or more drugs taken in combination. Both pharmacodynamic and pharmacokinetic interactions are possible between different drugs. This can lead to a change in the effectiveness of the drugs used [20], which makes pDDIs potentially dangerous. Drug effects can either be attenuated or potentiated, increasing the risk of treatment failure and side effects, respectively [21]. pDDIs are a significant but frequently underestimated risk factor for hospitalizations and secondary comorbidities [22,23]. It is estimated that between one and two percent of hospitalizations are caused by pDDIs [24]. To date, there is very limited information on the relevance of pDDIs in patients with MS. To our knowledge, there are no studies on pDDIs in patients with MS that were conducted in a large cohort.

The objective of our study was to investigate the prevalence of pDDIs as well as the degrees of pDDI severity in patients with MS. We compared patients with PP (PwP) and patients without PP (Pw/oP). PP status was evaluated from two different perspectives: one including only prescription drugs and one that also included over-the-counter (OTC) drugs. We aimed to find out the most frequently used drugs and the most often-occurring pDDIs. In addition, we provide estimates of the risks of PwP versus Pw/oP for having more severe pDDIs.

2. Materials and Methods

2.1. Study Population

This cross-sectional multicenter study was conducted at the Department of Neurology of the University Medical Center Rostock (Germany) and at the Department of Neurology of the Ecumenic Hainich Hospital Mühlhausen (Germany). In total, data of 627 patients with MS were collected in both medical centers from March 2017 to May 2020. Inclusion criteria were an age of at least 18 years and a diagnosis of CIS or MS according to the revised McDonald criteria [11]. Both inpatients and outpatients were asked to participate in this study. Data acquisition was performed during clinical routine appointments in case of outpatients and during a clinical stay (due to routine glucocorticosteroid pulse therapy, a recent relapse or progression of disability) in case of inpatients.

The study was approved by the ethics committees of the University of Rostock and of the Physicians' Chamber of Thuringia (permit numbers A 2014-0089 and A 2019-0048). Furthermore, our study was conducted according to the Declaration of Helsinki. All patients participated voluntarily and provided informed consent.

2.2. Gathered Data

We collected sociodemographic, clinical and pharmaceutical data of the 627 patients by assessing each patient's medical record and by conducting a clinical examination as well as a structured interview.

Sociodemographic data consisted of age, sex and partnership. Moreover, number of children and siblings, employment status, educational level and number of school years, as well as place of residence (divided into rural community, provincial town, medium-sized town or city) were recorded. Clinical data contained comorbidities, disease duration, age at MS onset, disease course (CIS, PPMS, RRMS or SPMS) and clinical disability according to Kurtzke's Expanded Disability Status Scale (EDSS) [25]. Comorbidities were ascertained

according to the definition by Moss et al. [26,27] through patient interviews and patient records and summarized into 16 comorbidity groups based on the affected organ system. Pharmaceutical data comprised each patient's medication schedule, including drug names and active agents, dosage and application form as well as the indication for every drug. Drugs were classified according to the anatomical therapeutic chemical (ATC) classification system. Drugs that were not only available on prescription as well as nutritional supplements were also included.

2.3. Drug Characterization

For drug classification, we collected additional data on all drugs to arrange them by the following criteria: OTC drugs and prescription-only drugs (Rx). Besides the indication, we also noted the treatment goal for each drug: DMDs, symptomatic relief, or treatment of comorbidities or other conditions (e.g., contraception). Drugs were also classified according to the intake interval. Long-term drugs are those permanently taken, either daily or in routine intervals, e.g., weekly or every three months, while drugs on demand (*pro re nata*, PRN) are those taken when needed to care for acute symptoms.

2.4. Polypharmacy

In our study, we differentiated between total PP and Rx PP. As it is the most common definition in the literature [1], we defined total PP as the simultaneous intake of at least five drugs (Rx and OTC drugs considered together). Rx PP was defined as the intake of at least five drugs prescribed by a doctor (neglecting OTC drugs that were not prescribed by a doctor).

2.5. Identification of Drug–Drug Interactions

To identify pDDIs, we used two different kinds of software: a clinical decision support software (CDSS) called *MediQ* and a drug–drug interaction database (DDID) called *Stockley's Interaction Checker*. Each patient's medication schedule was checked with *MediQ* and *Stockley's*. *MediQ* is a Swiss web-based interaction checker for drug–drug, drug–food, drug–alcohol and drug–polymorphism interactions. It includes more than 2000 active substances and more than 49,000 interactions [28]. The following pDDI categories are distinguished in *MediQ*: high danger, average danger, low danger, no danger of interaction and lack of evidence. *MediQ* is one of the most commonly used CDSS in the German-speaking area and has found to be the most complete in a study comparing five CDSS in German language [29]. To achieve greater coverage, we also used *Stockley's Interaction Checker* by the Royal Pharmaceutical Society, a British online tool based on the comprehensive and evidence-based compendium *Stockley's Drug Interactions*. This online tool contains information on drug–drug, drug–herb, drug–alcohol and drug–food interactions, with about 85,000 interactions listed in total [30]. In *Stockley's Interaction Checker*, there are the following severity rating categories: severe, moderate, mild and no interaction. As both databases are permanently updated, it is important to note that we checked the medication plans of our patients for pDDIs between May and November 2020.

2.6. Composite Rating of pDDI Severity Levels

To combine each pDDI's severity level from *MediQ* and *Stockley's Interaction Checker*, we allocated each severity rating to a numeric value: 3 for severe (*Stockley's*) or high danger (*MediQ*); 2 for moderate (*Stockley's*) or average danger (*MediQ*); 1 for mild (*Stockley's*) or low danger (*MediQ*); and 0 for no danger of interaction or lack of evidence. Then, for the combined severity grade, the numeric values of the severity levels of both databases were summed for each pDDI. A sum of ≤ 2 , 3, 4, 5 and 6 indicated a mild, mildly moderate, moderate, moderately severe and severe pDDI, respectively.

2.7. Statistics

Using SPSS Statistics version 27 (IBM) and R version 3.6 (R Foundation for Statistical Computing), the pseudonymized data were statistically analyzed. Counts and percentages were calculated for descriptive purposes. Measures of location and dispersion such as median, range, mean value and standard deviation were calculated as appropriate. Frequencies were also calculated to assess the prevalence of drugs used, pDDIs and pDDI severity levels. For comparing PwP and Pw/oP, statistical testing was applied. For numerical variables, we applied two-sample two-tailed Welch *t*-tests and Mann–Whitney U tests. For categorical variables, we used Fisher’s exact tests and chi-squared tests. The significance level was set at $\alpha = 0.05$. The analyses should be considered as exploratory. Bar charts and pie charts were created with Microsoft Excel version 16.49. Confidence intervals for proportions were calculated according to the Clopper–Pearson exact method and visualized using R version 3.6.

3. Results

3.1. Sociodemographic and Clinical Patient Profile

Of all 627 patients included, 70.3% were female and 29.7% were male (Table 1). The patients’ ages ranged from 19 to 86 years, with a mean of 48.6 years (standard deviation: 13.3 years). Most patients lived in a partnership (74.2%) and in a rural community (35.7%). Almost half of all patients had one sibling (48.6%) and at least two children (45.9%). On average, the patients went to school for 10.5 years. A subset of 63.5% of all patients were trained as a skilled worker. About half of all patients (48.5%) obtained disability pension at the time of the data acquisition. Among the patients analyzed, the median EDSS score was 3.5 (range 0 to 9.0) and the median disease duration was 10 years, with a median age of 35 years at disease onset. Most patients (66.2%) were diagnosed with a CIS (N = 27) or RRMS (N = 388). The number of comorbidities varied from zero to nine, with a median of one comorbidity besides MS.

3.2. Polypharmacy

By the definition of total PP, a slight majority of 53.3% of all patients had PP. According to our definition of Rx PP, 38.6% of the patients had PP, leaving 61.4% of Pw/oP. The sex ratios in all four groups (total PP, no total PP, Rx PP, no Rx PP) were nearly the same as in the total population. However, we found that PwP were, on average, significantly older than Pw/oP (*t*-test: $p < 0.001$) for total PP as well as for Rx PP (53.0 years vs. 43.6 years and 54.8 years vs. 44.7 years, respectively). PP was also associated with a significantly lower number of years in school (*t*-test: $p < 0.001$) and a lower educational level (chi-squared test: $p < 0.02$). Moreover, PwP were more than twice as likely to receive disability pension compared to Pw/oP (67.4% vs. 27.0% for total PP and 73.6% vs. 32.7% for Rx PP, respectively) and were employed more rarely (chi-squared test: $p < 0.001$). In PwP, the median EDSS score was significantly higher (4.5 vs. 2.0 for total PP; 5.0 vs. 2.5 for Rx PP, Mann–Whitney U test: $p < 0.001$ for both) and the median disease duration was longer (12.5 vs. 9 years for total PP; 14 vs. 9 years for Rx PP, Mann–Whitney U test: $p < 0.001$), indicating that PwP were typically at an advanced stage of MS than Pw/oP. The median number of comorbidities was also significantly higher in PwP in comparison to Pw/oP (Table 1).

3.3. Comorbidities

With a prevalence of 27.1%, cardiovascular comorbidities were most frequent among all patients, followed by psychiatric (19.3%), metabolic (17.7%), neurological and orthopedic comorbidities (both 12.4%; Supplementary Table S1). PwP (both total PP and Rx PP) were significantly more likely to have one of these aforementioned comorbidities than Pw/oP (Fisher’s exact test: $p \leq 0.027$). Moreover, gastrointestinal and ophthalmological comorbidities were also significantly more prevalent among PwP. PwP and Pw/oP had very different distributions of the numbers of comorbidities. For instance, the proportion of patients without any comorbidities was 3 to 4 times higher for Pw/oP than for PwP (Table 1).

Table 1. Sociodemographic, clinical and pharmaceutical data of patients with MS, stratified by polypharmacy status.

	All Patients		Total Polypharmacy		Rx Polypharmacy		p	
	N	Pw/P	Pw/oP	Pw/P	Pw/oP	Pw/oP		
	627	334 (53.3%)	293 (46.7%)	242 (38.6%)	385 (61.4%)			
			Sociodemographic data					
Sex							0.720 ^H	
Male	186 (29.7%)	101 (30.2%)	85 (29.0%)	74 (30.6%)	112 (29.1%)			
Female	441 (70.3%)	233 (69.8%)	208 (71.0%)	168 (69.4%)	273 (70.9%)			
Age (years)							<0.001 ^t	
19–86 ^K	48.6 (13.3) ^a	20–86 ^K 53.0 (12.7) ^a	19–74 ^K 43.6 (12.2) ^a	24–86 ^K 54.8 (12.1) ^a	19–75 ^K 44.7 (12.5) ^a		<0.001 ^t	
School years							<0.001 ^t	
6–18 ^K	10.5 (1.3) ^a	6–14 ^K 10.3 (1.2) ^a	8–18 ^K 10.7 (1.3) ^a	6–14 ^K 10.2 (1.2) ^a	8–18 ^K 10.7 (1.3) ^a		<0.001 ^t	
Educational level							0.019 ^{Chi}	
No training	19 (3.0%)	8 (2.4%)	11 (3.8%)	7 (2.9%)	12 (3.1%)			
Skilled worker	398 (63.5%)	229 (68.6%)	169 (57.7%)	173 (71.5%)	225 (58.4%)			
Technical college	89 (14.2%)	46 (13.8%)	43 (14.7%)	33 (13.6%)	56 (14.5%)			
University	121 (19.3%)	51 (15.3%)	70 (23.9%)	29 (12.0%)	92 (23.9%)			
Employment status							<0.001 ^{Chi}	
In training	7 (1.1%)	1 (0.3%)	6 (2.0%)	0 (0.0%)	7 (1.8%)			
In studies	6 (1.0%)	0 (0.0%)	6 (2.0%)	0 (0.0%)	6 (1.6%)			
Employed	269 (42.9%)	92 (27.5%)	177 (60.4%)	53 (21.9%)	216 (56.1%)			
Unemployed	25 (4.0%)	10 (3.0%)	15 (5.1%)	7 (2.9%)	18 (4.7%)			
Disability-pensioned	304 (48.5%)	225 (67.4%)	79 (27.0%)	178 (73.6%)	126 (32.7%)			
Other	16 (2.6%)	6 (1.8%)	10 (3.4%)	4 (1.7%)	12 (3.1%)		0.305 ^H	
Partnership								
No	162 (25.8%)	86 (25.7%)	76 (25.9%)	68 (28.1%)	94 (24.4%)			
Yes	465 (74.2%)	248 (74.3%)	217 (74.1%)	174 (71.9%)	291 (75.6%)		0.962 ^{Chi}	
Place of Residence								
Rural community	224 (35.7%)	119 (35.6%)	105 (35.8%)	89 (36.8%)	135 (35.1%)			
Provincial town	108 (17.2%)	63 (18.9%)	45 (15.4%)	42 (17.4%)	66 (17.1%)			
Medium-sized town	112 (17.9%)	64 (19.2%)	48 (16.4%)	43 (17.8%)	69 (17.9%)			
City	183 (29.2%)	88 (26.3%)	95 (32.4%)	68 (28.1%)	115 (29.9%)			
Number of children							0.056 ^U	
0	169 (27.0%)	77 (23.1%)	92 (31.4%)	54 (22.3%)	115 (29.9%)			
1	170 (27.1%)	98 (29.3%)	72 (24.6%)	68 (28.1%)	102 (26.5%)			
≥2	288 (45.9%)	159 (47.6%)	129 (44.0%)	120 (49.6%)	168 (43.6%)			
Number of siblings							0.018 ^U	
0	71 (11.3%)	33 (9.9%)	38 (13.0%)	26 (10.7%)	45 (11.7%)			
1	305 (48.6%)	160 (47.9%)	145 (49.5%)	103 (42.6%)	202 (52.5%)			
≥2	251 (40.0%)	141 (42.2%)	110 (37.5%)	113 (46.7%)	138 (35.8%)			
			Clinical data					

Table 1. Contd.

	All Patients			Total Polypharmacy			Rx Polypharmacy			p	
	0–9 K	10 ^b	35 ^b	PwP	Pw/oP	Pw/oP	PwP	Pw/oP	Pw/oP		
EDSS	0–9 K	3.5 ^b	0–9 K	4.5 ^b	0–7.5 K	2.0 ^b	0–9 K	5.0 ^b	0–7.5 K	2.5 ^b	<0.001 U
Disease duration (years)	0–52 K	10 ^b	0–50 K	12.5 ^b	0–52 K	9 ^b	0–50 K	14 ^b	0–52 K	9 ^b	<0.001 U
Age at MS onset	9–75 K	35 ^b	9–75 K	38 ^b	12–62 K	32 ^b	9–75 K	39 ^b	12–69 K	33 ^b	<0.001 U
Disease course											<0.001 Chi
CIS/RRMS	415 (66.2%)	158 (47.3%)	158 (47.3%)	257 (87.7%)	257 (87.7%)	91 (37.6%)	91 (37.6%)	324 (84.2%)	324 (84.2%)		<0.001 Chi
SPMS	154 (24.6%)	125 (37.4%)	125 (37.4%)	29 (9.9%)	29 (9.9%)	109 (45.0%)	109 (45.0%)	45 (11.7%)	45 (11.7%)		<0.001 U
PPMS	58 (9.3%)	51 (15.3%)	51 (15.3%)	7 (2.4%)	7 (2.4%)	42 (17.4%)	42 (17.4%)	16 (4.2%)	16 (4.2%)		<0.001 U
Comorbidities	0–9 K	1 ^b	0–9 K	2 ^b	0–5 K	1 ^b	0–9 K	3 ^b	0–7 K	1 ^b	<0.001 U
0	184 (29.3%)	46 (13.8%)	46 (13.8%)	138 (47.1%)	138 (47.1%)	24 (9.9%)	24 (9.9%)	160 (41.6%)	160 (41.6%)		<0.001 U
1	150 (23.9%)	60 (18.0%)	60 (18.0%)	90 (30.7%)	90 (30.7%)	39 (16.1%)	39 (16.1%)	111 (28.8%)	111 (28.8%)		<0.001 U
2	122 (19.5%)	76 (22.8%)	76 (22.8%)	46 (15.7%)	46 (15.7%)	50 (20.7%)	50 (20.7%)	72 (18.7%)	72 (18.7%)		<0.001 U
3	82 (13.1%)	71 (21.3%)	71 (21.3%)	11 (3.8%)	11 (3.8%)	58 (24.0%)	58 (24.0%)	24 (6.2%)	24 (6.2%)		<0.001 U
4	50 (8.0%)	44 (13.2%)	44 (13.2%)	6 (2.0%)	6 (2.0%)	35 (14.5%)	35 (14.5%)	15 (3.9%)	15 (3.9%)		<0.001 U
≥5	39 (6.2%)	37 (11.1%)	37 (11.1%)	2 (0.7%)	2 (0.7%)	36 (14.9%)	36 (14.9%)	3 (0.8%)	3 (0.8%)		<0.001 U
Pharmaceutical data											
Number of total drugs taken	0–19 K	5.3 (3.3) ^c	5–19 K	7.8 (2.7) ^c	0–4 K	2.6 (1.1) ^c	5–19 K	8.5 (2.7) ^c	0–9 K	3.3 (1.7) ^c	<0.001 t
0–4	293 (46.7%)	0 (0.0%)	0 (0.0%)	293 (100.0%)	293 (100.0%)	0 (0.0%)	0 (0.0%)	293 (76.1%)	293 (76.1%)		<0.001 t
5–9	261 (41.6%)	261 (78.1%)	261 (78.1%)	0 (0.0%)	0 (0.0%)	169 (69.8%)	169 (69.8%)	92 (23.9%)	92 (23.9%)		<0.001 t
≥10	73 (11.6%)	73 (21.9%)	73 (21.9%)	0 (0.0%)	0 (0.0%)	73 (30.2%)	73 (30.2%)	0 (0.0%)	0 (0.0%)		<0.001 t
Duration of use	0–16 K	4.6 (3.1) ^c	1–16 K	6.7 (2.7) ^c	0–4 K	2.2 (1.1) ^c	1–16 K	7.4 (2.7) ^c	0–9 K	2.8 (1.7) ^c	<0.001 t
Long-term drugs	0–7 K	0.8 (1.2) ^c	0–7 K	1.1 (1.4) ^c	0–4 K	0.4 (0.7) ^c	0–7 K	1.2 (1.4) ^c	0–6 K	0.6 (0.9) ^c	<0.001 t
Rx vs. OTC											<0.001 t
Rx drugs	0–18 K	4.2 (3.0) ^c	1–18 K	6.2 (2.8) ^c	0–4 K	1.9 (1.0) ^c	5–18 K	7.3 (2.4) ^c	0–4 K	2.2 (1.2) ^c	<0.001 t
OTC drugs	0–8 K	1.1 (1.3) ^c	0–8 K	1.6 (1.4) ^c	0–3 K	0.6 (0.8) ^c	0–6 K	1.2 (1.3) ^c	0–8 K	1.1 (1.3) ^c	0.206 t
Drug purpose											<0.001 t
DMD	0–2 K	0.9 (0.4) ^c	0–2 K	0.9 (0.4) ^c	0–2 K	0.8 (0.4) ^c	0–2 K	0.9 (0.4) ^c	0–2 K	0.8 (0.4) ^c	<0.001 t
Symptomatic drugs	0–9 K	2.0 (2.0) ^c	0–9 K	3.1 (2.0) ^c	0–3 K	0.7 (0.9) ^c	0–9 K	3.3 (2.0) ^c	0–9 K	1.2 (1.4) ^c	<0.001 t
Comorbidity drugs	0–14 K	2.5 (2.4) ^c	0–14 K	3.8 (2.6) ^c	0–4 K	1.0 (0.9) ^c	0–14 K	4.3 (2.7) ^c	0–7 K	1.3 (1.3) ^c	<0.001 t

Total polypharmacy = intake of at least five drugs (of any kind). Rx polypharmacy = intake of at least five drugs that were prescribed (neglecting OTC drugs). ^a—mean value (standard deviation); ^b—median; ^c—average number of drugs taken per patient (standard deviation); Chi—chi-squared test; CIS—clinically isolated syndrome; DMD—disease-modifying drug; EDSS—Expanded Disability Status Scale; FI—Fisher's exact test; MS—multiple sclerosis; N—number of patients; OTC—over the counter; *p*—*p*-value for comparing patients with and without polypharmacy; PwP—patients with polypharmacy; Pw/oP—patients without polypharmacy; PPMS—primary progressive multiple sclerosis; PRN—*pro re nata* (on demand); R—range; RRMS—relapsing-remitting multiple sclerosis; Rx—prescription; t—two-sample two-tailed Welch *t*-test; U—Mann–Whitney U test.

3.4. Drug Profile

The number of drugs taken per patient ranged from 0 to 19, with a mean of 5.3 drugs per patient (Table 1). A subset of 46.7% of the patients took zero to four drugs (no total PP) and 53.3% took at least five drugs (total PP). More than nine drugs were taken by 11.6% of all patients, resulting in so-called excessive PP.

In total, the 627 patients used 3341 drugs, counted with repetitions (Table 2). Of all drugs, 85.5% were long-term drugs and 14.5% were PRN drugs. As many as 78.7% of all drugs taken were on prescription. Those drugs were significantly more often used by PwP (both total PP and Rx PP), while OTC drugs accounted for a higher proportion in Pw/oP as compared to PwP (24.7% vs. 20.3% and Fisher's exact test: $p = 0.011$ for total PP, 32.6% vs. 14.3% and Fisher's exact test: $p < 0.001$ for Rx PP). A subset of 46.6% of all drugs were used to treat comorbidities. About 37.5% of all drugs were symptomatic drugs and 15.9% were DMDs. Symptomatic and comorbidity drugs were more frequently used by PwP than by Pw/oP (symptomatic drugs: 39.9% vs. 29.0% for total PP, comorbidity drugs: 48.6% vs. 39.9% for total PP, respectively).

Table 2. Total number of all recorded medications (counted with repetitions), subdivided by drug category and polypharmacy status of the patients with MS (N = 627).

Drug Category	Total Number of Drugs	Total Polypharmacy			Rx Polypharmacy		
		PwP	Pw/oP	<i>p</i>	PwP	Pw/oP	<i>p</i>
All	3341 (100%)	2591 (77.6%)	750 (22.4%)		2060 (61.7%)	1281 (38.3%)	
Duration of use				0.176 ^{Fi}			0.013 ^{Fi}
Long-term drugs	2855 (85.5%)	2226 (85.9%)	629 (83.9%)		1785 (86.7%)	1070 (83.5%)	
PRN drugs	486 (14.5%)	365 (14.1%)	121 (16.1%)		275 (13.3%)	211 (16.5%)	
Rx vs. OTC				0.011 ^{Fi}			<0.001 ^{Fi}
Rx drugs	2630 (78.7%)	2065 (79.7%)	565 (75.3%)		1766 (85.7%)	864 (67.4%)	
OTC drugs	711 (21.3%)	526 (20.3%)	185 (24.7%)		294 (14.3%)	417 (32.6%)	
Drug purpose				<0.001 ^{Chi}			<0.001 ^{Chi}
DMD	530 (15.9%)	297 (11.5%)	233 (31.1%)		223 (10.8%)	307 (24.0%)	
Symptomatic drugs	1253 (37.5%)	1035 (39.9%)	218 (29.0%)		796 (38.6%)	457 (35.7%)	
Comorbidity drugs	1558 (46.6%)	1259 (48.6%)	299 (39.9%)		1041 (50.6%)	517 (40.3%)	

Total polypharmacy = intake of at least five drugs (of any kind). Rx polypharmacy = intake of at least five drugs that were prescribed (neglecting OTC drugs). ^{Chi}—chi-squared test; DMD—disease-modifying drug; MS—multiple sclerosis; OTC—over the counter; *p*—*p*-value for comparing patients with and without polypharmacy; PwP—patients with polypharmacy; Pw/oP—patients without polypharmacy; PRN—*pro re nata* (on demand); Rx—prescription.

The most often used non-DMD was cholecalciferol, which was taken by 41.6% of all patients, followed by pantoprazole (28.4%) and enoxaparin (20.3%). These medications were used significantly more often by PwP than by Pw/oP (Table 3). A total of 123 patients (19.6%) received methylprednisolone. A frequently used DMD was interferon beta-1a, which was predominantly applied by Pw/oP (13.3% in Pw/oP vs. 7.5% in PwP for total PP, Fisher's exact test: $p = 0.018$; 13.0% in Pw/oP vs. 5.8% in PwP for Rx PP, Fisher's exact test: $p = 0.004$). The DMD glatiramer acetate was also taken significantly more frequently by Pw/oP than by PwP (Fisher's exact test: $p = 0.012$ for total PP, $p = 0.023$ for Rx PP) (Table 3).

Most patients used drugs for disorders related to alimentary tract and metabolism (e.g., proton pump inhibitors or antidiabetic drugs); 68.9% of all patients took at least one drug from this group. The second most commonly taken medication group comprised anti-neoplastic and immunomodulating agents (62.2%), to which interferons and mitoxantrone belong, followed by drugs affecting the nervous system (54.1%). The latter included, for example, analgesics such as acetylsalicylic acid or acetaminophen, and antidepressants such as citalopram.

Table 3. Most frequently used non-DMDs and DMDs among MS patients with and without polypharmacy.

N	All Patients			Total Polypharmacy			Rx Polypharmacy		
	N	Pw/oP	p ^{FI}	N	Pw/oP	p ^{FI}	N	Pw/oP	p ^{FI}
Most used non-DMDs									
Cholecalciferol	627	334 (53.3%)		293 (46.7%)	242 (38.6%)		385 (61.4%)		
Pantoprazole	261 (41.6%)	178 (53.3%)	<0.001	83 (28.3%)	125 (51.7%)	<0.001	136 (35.3%)		<0.001
Enoxaparin	178 (28.4%)	155 (46.4%)	<0.001	23 (7.8%)	144 (59.5%)	<0.001	34 (8.8%)		<0.001
Ibuprofen	127 (20.3%)	114 (34.1%)	<0.001	13 (4.4%)	105 (43.3%)	<0.001	22 (5.7%)		<0.001
Baclofen	105 (16.7%)	61 (18.3%)	0.286	44 (15.0%)	41 (16.9%)		64 (16.6%)		0.913
Levothyroxine	78 (12.4%)	72 (21.6%)	<0.001	6 (2.0%)	68 (28.1%)	<0.001	10 (2.6%)		<0.001
Cyanocobalamin	75 (12.0%)	51 (15.3%)	0.007	24 (8.2%)	41 (16.9%)		34 (8.8%)		0.003
Zopiclone	66 (10.5%)	46 (13.8%)	0.006	20 (6.8%)	27 (11.2%)		39 (10.1%)		0.690
Magnesium	65 (10.4%)	58 (17.4%)	<0.001	7 (2.4%)	53 (21.9%)	<0.001	12 (3.1%)		<0.001
Acetylsalicylic acid	60 (9.6%)	45 (13.5%)	<0.001	15 (5.1%)	21 (8.7%)		39 (10.1%)		0.580
Methylprednisolone	55 (8.8%)	48 (14.4%)	<0.001	7 (2.4%)	41 (16.9%)	<0.001	14 (3.6%)		<0.001
DMDs (all, incl. methylprednisolone)									
Interferon beta-1a	123 (19.6%)	110 (32.9%)	<0.001	13 (4.4%)	101 (41.7%)	<0.001	22 (5.7%)		<0.001
Glatiramer acetate	64 (10.2%)	25 (7.5%)	0.018	39 (13.3%)	14 (5.8%)		50 (13.0%)		0.004
Natalizumab	57 (9.1%)	21 (6.3%)	0.012	36 (12.3%)	14 (5.8%)		43 (11.2%)		0.023
Fingolimod	47 (7.5%)	18 (5.4%)	0.034	29 (9.9%)	9 (3.7%)		38 (9.9%)		0.005
Teriflunomide	41 (6.5%)	21 (6.3%)	0.872	20 (6.8%)	15 (6.2%)		26 (6.8%)		0.869
Dimethyl fumarate	36 (5.7%)	19 (5.7%)	1.000	17 (5.8%)	11 (4.5%)		25 (6.5%)		0.379
Mitoxantrone	32 (5.1%)	10 (3.0%)	0.011	22 (7.5%)	8 (3.3%)		24 (6.2%)		0.135
Ocrelizumab	28 (4.5%)	15 (4.5%)	1.000	13 (4.4%)	11 (4.5%)		17 (4.4%)		1.000
Interferon beta-1b	27 (4.3%)	25 (7.5%)	<0.001	2 (0.7%)	19 (7.9%)	<0.001	8 (2.1%)		0.001
Alentuzumab	23 (3.7%)	9 (2.7%)	0.203	14 (4.8%)	7 (2.9%)		16 (4.2%)		0.515
Immunoglobulin G	20 (3.4%)	5 (1.5%)	0.012	15 (5.1%)	2 (0.8%)		18 (4.7%)		0.009
Cladribine	7 (1.1%)	3 (0.3%)	0.711	4 (1.4%)	0 (0.0%)		7 (1.8%)		0.047
Azathioprine	6 (1.0%)	2 (0.6%)	0.426	4 (1.4%)	2 (0.8%)		4 (1.0%)		1.000
Rituximab	4 (0.6%)	2 (0.6%)	1.000	2 (0.7%)	1 (0.4%)		3 (0.8%)		1.000
	2 (0.3%)	1 (0.3%)	1.000	1 (0.3%)	0 (0.0%)		2 (0.5%)		0.525

Total polypharmacy = intake of at least five drugs (of any kind). Rx polypharmacy = intake of at least five drugs that were prescribed (neglecting OTC drugs). DMD—disease-modifying drug for the treatment of MS; FI—Fisher's exact test; MS—multiple sclerosis; N—number of patients; P—p-value for comparing patients with and without polypharmacy; Pw/oP—patients with polypharmacy; Pw/oP—patients without polypharmacy; Rx—prescription.

3.5. Drug–Drug Interactions

For the 627 patients analyzed, we detected a total of 2887 pDDIs (counted with repetitions). These resulted from 1424 different pDDIs (counted without repetitions) that were related to 267 different active agents (Supplementary Table S3). For 63.8% of all patients, at least one pDDI was identified. The number of pDDIs per patient ranged from 0 to 65, with a mean value of 4.6 pDDIs per patient. Of all 2887 recorded pDDIs, 2745 (95.1%) applied to patients with total PP, while they only made up around half of all patients (53.3%). With regard to Rx PP, the PwP group (38.6% of all patients) accounted for 2550 (88.3%) of all pDDIs. Accordingly, the average number of pDDIs differed considerably between PwP and Pw/oP (Rx PP as well as total PP). In Pw/oP, the average number of pDDIs was 0.5 ± 1.0 (total PP) and 0.9 ± 1.4 (Rx PP) per patient; in PwP, it was 8.2 ± 10.7 (total PP) and 10.5 ± 10.4 (Rx PP) (Figure 1).

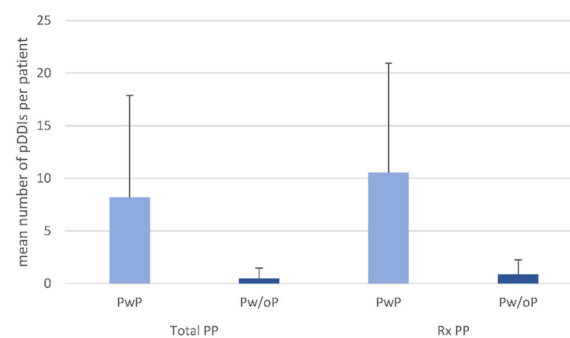


Figure 1. Average number of pDDIs per patient with MS, stratified by PP status and type of PP. The patients were classified by PP status according to total PP (intake of at least five drugs of any kind) and Rx PP (intake of at least five drugs only available on prescription). Standard deviations are displayed as error bars. The average number of pDDIs was higher in PwP compared with Pw/oP, for both total PP (8.2 ± 9.7 versus 0.5 ± 1.0) and Rx PP (10.5 ± 10.4 versus 0.9 ± 1.4). MS—multiple sclerosis; pDDI—potential drug–drug interaction; PP—polypharmacy; PwP—patients with polypharmacy; Pw/oP—patients without polypharmacy; Rx—only available on prescription.

The 2887 pDDIs that were identified consisted of mainly mild pDDIs (65.4%) (Figure 2). Mildly moderate pDDIs accounted for 17.7% and moderate pDDIs for 12.9% of all pDDIs. Moderately severe pDDIs made up a rather small percentage of 3.7%. Only 7 of all 2887 pDDIs (0.2%) were rated as severe by both softwares.

Of all 627 patients, 57.9% had at least one mild pDDI, 27.8% had at least one moderate pDDI and 11.0% had at least one moderately severe pDDI (Table 4). For 36.2% of all patients, we found no pDDI at all. Evidently, pDDIs were much more prevalent in PwP than in Pw/oP, independently of the degree of pDDI severity. For total PP, we found that 88.9% of all PwP had at least one mild pDDI, while this applied to only 22.5% of all Pw/oP (Fisher’s exact test: $p < 0.001$). Similar numbers were found for Rx PP. Moreover, more than half of the PwP (52.4% for total PP and 64.9% for Rx PP) had at least one mildly moderate pDDI, while less than 10% of the Pw/oP had at least one mildly moderate pDDI (total PP and Rx PP, Fisher’s exact test: $p < 0.001$ for both) (Table 4). The risk of pDDIs increased with the number of drugs used simultaneously. Patients taking five medications (Rx and OTC) already had a 79.5% risk of having a mild pDDI. While an intake of five or fewer drugs resulted in a risk of having a moderately severe pDDI lower than 10%, the likelihood of having a moderately severe pDDI increased above 20% when 10 or more medications were used (Figure 3).

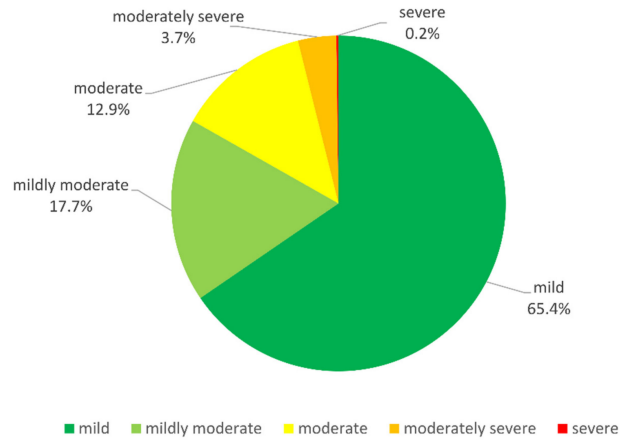


Figure 2. Distribution of severity levels of pDDIs in patients with MS. For the 627 patients, we recorded 2887 pDDIs in total (counted with repetitions) based on *MediQ* and *Stockley’s drug interaction checker*. MS—multiple sclerosis; pDDI—potential drug–drug interaction.

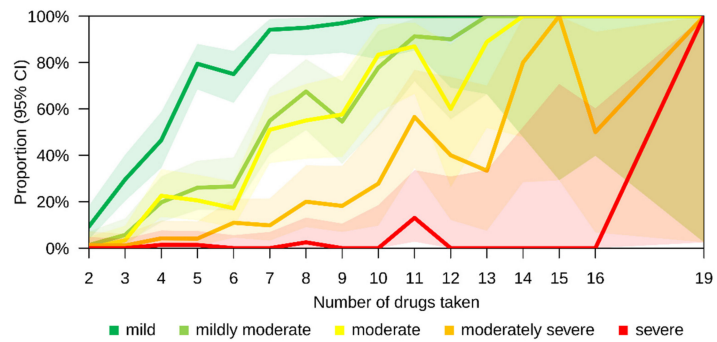


Figure 3. Proportion of patients with MS with at least one pDDI for each severity level and depending on the number of drugs used. The composite rating of pDDI severities was based on *MediQ* and *Stockley’s drug interaction checker*. Both prescription and over-the-counter drugs were considered for this plot. CI—confidence interval; MS—multiple sclerosis; pDDI—potential drug–drug interaction.

Table 4. Prevalence of pDDIs in the patients with MS.

	All Patients	Total Polypharmacy			Rx Polypharmacy		
		PwP	Pw/oP	<i>p</i> ^{Fi}	PwP	Pw/oP	<i>p</i> ^{Fi}
N	627	334 (53.3%)	293 (46.7%)		242 (38.6%)	385 (61.4%)	
Severity level							
Mild	363 (57.9%)	297 (88.9%)	66 (22.5%)	<0.001	225 (93.0%)	138 (35.8%)	<0.001
Mildly moderate	195 (31.1%)	175 (52.4%)	20 (6.8%)	<0.001	157 (64.9%)	38 (9.9%)	<0.001
Moderate	174 (27.8%)	155 (46.4%)	19 (6.5%)	<0.001	140 (57.9%)	34 (8.8%)	<0.001
Moderately severe	69 (11.0%)	64 (19.2%)	5 (1.7%)	<0.001	61 (25.2%)	8 (2.1%)	<0.001
Severe	7 (1.1%)	6 (1.8%)	1 (0.3%)	0.129	5 (2.1%)	2 (0.5%)	0.114
No pDDI at all	227 (36.2%)	22 (6.6%)	205 (70.0%)	<0.001	7 (2.9%)	220 (57.1%)	<0.001

Each patient who had at least one pDDI of a given category was counted. Note that the patients could have several pDDIs of different severities at the same time. The level of severity of pDDIs was assessed based on *MediQ* and *Stockley’s drug interaction checker*. Total polypharmacy = intake of at least five drugs (of any kind). Rx polypharmacy = intake of at least five drugs that were prescribed (neglecting OTC drugs). ^{Chi}—chi-squared test; ^{Fi}—Fisher’s exact test; MS—multiple sclerosis; N—number of patients; *p*—*p*-value for comparing patients with and without polypharmacy; pDDI—potential drug–drug interaction; PwP—patients with polypharmacy; Pw/oP—patients without polypharmacy; Rx—prescription.

By examining the prescription status of each drug in a pDDI, we found that 77.3% of all pDDIs consisted of two Rx drugs; 19.0% of one Rx drug and one OTC drug; and 3.7% of two OTC drugs (Table 5). The most frequent pDDI was the interaction between cholecalciferol and magnesium, which was rated as a mild interaction (Table 6). It applied to 5.7% of all patients. Another common pDDI was between acetylsalicylic acid and methylprednisolone, which affected 3.3% of all patients and was rated as a moderate interaction. The seven severe pDDIs detected concerned seven different patients (1.1% of all patients). Remarkably, all of the seven severe pDDIs contained citalopram, which was used in combination with one of the following: ciprofloxacin, doxepin, flecainide, levofloxacin, ondansetron and quetiapine. The pDDI of citalopram and ondansetron was found for two patients. A complete list of all pDDIs is provided in Supplementary Table S3.

Patients with at least one comorbidity from the cardiovascular, neurological, orthopedic or psychiatric group were significantly more likely to have at least one pDDI of any severity than those without a comorbidity from these specific groups (Supplementary Table S2). Of those with a cardiovascular comorbidity (e.g., coronary heart disease), 78.2% had at least one pDDI, compared with 58.4% of those without a cardiovascular comorbidity (Fisher's exact test: $p < 0.001$). Similar differences in the odds of having at least one pDDI were noted when comparing patients with and without psychiatric comorbidity (85.1% vs. 58.7%), neurological comorbidity (76.9% vs. 61.9%) and orthopedic comorbidity (80.8% vs. 61.4%).

Table 5. Distribution of pDDIs depending on severity level and prescription.

	Total Number of pDDIs Recorded	Rx-Rx	Rx-OTC	OTC-OTC	p^{Chi}
N	2887	2231 (77.3%)	549 (19.0%)	107 (3.7%)	
Severity level					<0.001
Mild	1889 (65.4%)	1469 (65.8%)	327 (59.6%)	93 (86.9%)	
Mildly moderate	511 (17.7%)	417 (18.7%)	85 (15.5%)	9 (8.4%)	
Moderate	373 (12.9%)	249 (11.2%)	120 (21.9%)	4 (3.7%)	
Moderately severe	107 (3.7%)	89 (4.0%)	17 (3.1%)	1 (0.9%)	
Severe	7 (0.2%)	7 (0.3%)	0 (0.0%)	0 (0.0%)	

The pDDIs were categorized by severity and whether they contained Rx and/or OTC drugs. The level of severity of pDDIs was assessed based on *MediQ* and *Stockley's* drug interaction checker. Rx-Rx, Rx-OTC and OTC-OTC relate to the kind of drugs the pDDI was made up of. ^{Chi}—chi-squared test; N—number of pDDIs; OTC—over the counter; p — p -value for comparing the proportions of the different pDDI categories; pDDI—potential drug–drug interaction; Rx—prescription.

Table 6. The most common pDDIs in patients with MS.

Drug 1	Drug 2	pDDI Severity	Total Amount (N = 627)	Total Polypharmacy		Rx Polypharmacy	
				Amount in Pw/oP (N = 334)	Amount in Pw/oP (N = 293)	Amount in PwP (N = 242)	Amount in Pw/oP (N = 385)
pDDIs of non-DMDs							
Cholecalciferol	Magnesium	mild	36 (5.7%)	30 (9.0%)	6 (2.0%)	15 (6.2%)	21 (5.5%)
Cyanocobalamin	Pantoprazole	mild	27 (4.3%)	25 (7.5%)	2 (0.7%)	23 (9.5%)	4 (1.0%)
Calcium	Cholecalciferol	mild	26 (4.1%)	25 (7.5%)	1 (0.3%)	22 (9.1%)	4 (1.0%)
Levothyroxine	Pantoprazole	mildly moderate	23 (3.7%)	22 (6.6%)	1 (0.3%)	22 (9.1%)	1 (0.3%)
Acetylsalicylic acid	Enoxaparin	moderate	21 (3.3%)	20 (6.0%)	1 (0.3%)	19 (7.9%)	2 (0.5%)
Cholecalciferol	Simvastatin	mild	20 (3.2%)	19 (5.7%)	1 (0.3%)	19 (7.9%)	1 (0.3%)
Baclofen	Fampridine	mild	20 (3.2%)	19 (5.7%)	1 (0.3%)	17 (7.0%)	3 (0.8%)
Cholecalciferol	Prednisolone	mild	18 (2.9%)	18 (5.4%)	0 (0.0%)	15 (6.2%)	3 (0.8%)
Pantoprazole	Torasemide	mild	18 (2.9%)	18 (5.4%)	0 (0.0%)	18 (7.4%)	0 (0.0%)
Cyanocobalamin	Folic acid	mild	17 (2.7%)	12 (3.6%)	5 (1.7%)	8 (3.3%)	9 (2.3%)
pDDIs of DMDs incl. methylprednisolone							
Acetylsalicylic acid	Methylprednisolone	moderate	21 (3.3%)	20 (6.0%)	1 (0.3%)	19 (7.9%)	2 (0.5%)
Ibuprofen	Methylprednisolone	mildly moderate	14 (2.2%)	13 (3.9%)	1 (0.3%)	13 (5.4%)	1 (0.3%)
Methylprednisolone	Ramipril	mild	12 (1.9%)	12 (3.6%)	0 (0.0%)	12 (5.0%)	0 (0.0%)
Citalopram	Methylprednisolone	moderately severe	10 (1.6%)	10 (3.0%)	0 (0.0%)	10 (4.1%)	0 (0.0%)
Methylprednisolone	Torasemide	mild	10 (1.6%)	10 (3.0%)	0 (0.0%)	10 (4.1%)	0 (0.0%)
Dipyron	Methylprednisolone	moderate	9 (1.4%)	9 (2.7%)	0 (0.0%)	9 (3.7%)	0 (0.0%)
Methylprednisolone	Sulfafenacin	mildly moderate	9 (1.4%)	9 (2.7%)	0 (0.0%)	8 (3.3%)	1 (0.3%)
Citalopram	Fingolimod	moderately severe	7 (1.1%)	5 (1.5%)	2 (0.7%)	3 (1.2%)	4 (1.0%)
Mitoxantrone	Ondansetron	mildly moderate	7 (1.1%)	4 (1.2%)	3 (1.0%)	3 (1.2%)	4 (1.0%)
Interferon beta-1a	Ramipril	mildly moderate	7 (1.1%)	5 (1.5%)	2 (0.7%)	4 (1.7%)	3 (0.8%)

Shown are the 10 most frequently detected interactions with and without the involvement of DMDs. The level of severity of pDDIs was assessed based on *MediQ* and *Stockley's* drug interaction checker. Total polypharmacy = intake of at least five drugs (of any kind). Rx polypharmacy = intake of at least five drugs that were prescribed (neglecting OTC drugs). DMD—disease-modifying drug for the treatment of MS; MS—multiple sclerosis; N—number of patients; pDDI—potential drug–drug interaction; PwP—patients with polypharmacy; Pw/oP—patients without polypharmacy; Rx—prescription.

4. Discussion

The aim of this study was to determine the extent of PP as well as the prevalence and severity of pDDIs among MS patients. As pDDIs are generally underestimated as a problem by both physicians and patients, it is important to give them more attention, especially in patients with chronic diseases such as MS. For this purpose, we conducted a comprehensive evaluation of the pharmaceutical data of patients with MS with regard to the type and number of drugs taken. PP is a common consequence of the extensive drug therapy often required in chronic diseases, and the higher likelihood of pDDIs resulting from this can lead to detrimental effects. This study is one of the first to evaluate the prevalence and risk of pDDIs in patients with MS and the association between PP and pDDI occurrence.

To our knowledge, there were no previous large-scale studies that addressed the issue of pDDIs in patients with MS until today. We previously evaluated pDDIs in MS patients, but this study was focused on a rather small group of women at childbearing age [31]. Comparisons to other chronic neurological or autoimmune diseases are difficult because the majority of studies dealing with pDDIs and PP were conducted in cohorts of elderly patients or nursing home residents [32,33]. These cohorts therefore have a much higher average age, more comorbidities and thus a higher average number of drugs used, resulting in higher prevalence rates of PP and pDDIs, which makes them hardly comparable to our patient cohort. This demonstrates the necessity of our study, as the issue of pDDIs is rarely discussed in younger and middle-aged patients. There is, however, a study from 2001 on the prevalence of pDDIs in the general population in Sweden, based on records on all prescriptions handed out in Swedish pharmacies [34]. The authors found that 13.6% of all prescriptions included at least one pDDI. If this cohort is considered representative of the general population then we can say, by comparing our results (63.8%) to theirs (13.6%), that patients with MS have an approximately 4.5 times higher chance of having at least one pDDI than the general population.

Of all 2887 pDDIs in our study, only seven were severe (0.2%). All of them contained citalopram as one of the interacting drugs. This suggests that the prescription of citalopram is associated with an increased risk of severe pDDIs as compared to other antidepressants. The frequent occurrence of citalopram in pDDIs—and especially those that are rated as severe—was also documented in a study on pDDIs among patients with dementia [35].

A unique feature of our study are the detailed drug data that were obtained and analyzed. Not only Rx and OTC drugs but also herbal and nutritional supplements were recorded and entered into the interaction software. OTC drugs were included in 22.7% of all pDDIs of our patients. In other studies, non-Rx medications were usually not counted [36] or there was no information on their use because they are often not considered relevant when evaluating pDDIs. However, our data showed that neglecting OTC drugs as part of some patients' medication plan means that a large number of pDDIs are overlooked. The same applies to medications that were only temporarily taken by the patients, such as antibiotics, which were left out in a Danish study addressing the topic of PP [33]. We included all medications that the patients were taking at the time of the interview, regardless of type and duration of their use. We suggest that OTC drugs, supplements and self-medication should be generally included in the assessment of pDDIs.

The negative effects of PP have been closely studied in the past. PP poses a threat to patients by increasing the risk of avoidable negative outcomes [37,38]. Noncompliance and nonadherence to medication, as well as the risk of adverse drug reactions [39], are issues related to the number of drugs that need to be taken regularly [40–42]. PP is positively correlated to the risk of pDDIs [43], thereby provoking a higher number of total pDDIs as well as severe pDDIs. Overall, the quality of life of PwP is negatively influenced by PP [44]. Another consequence of PP and pDDIs are higher costs of healthcare [32,36]. It is estimated that between one and two percent of hospitalizations are caused by pDDIs [24], which is an avoidable financial burden to the healthcare system. In our cohort, we found that about 95% of all pDDIs occurred in patients with total PP, even though those patients made up only around half of all patients. Patients with Rx PP (38.6%) accounted for 88.3%

of all pDDIs. This is highly relatable to a Swedish register-based study [45], which found that individuals taking five or more prescription drugs (that is, Rx PP) made up almost 80% of the total acquisition cost of Sweden's drugs while representing only around 25% of the population. Note that these are only acquisition costs for dispensed prescription drugs, thus hospitalization and costs for any other consequences were not included. Similar circumstances may be assumed in Germany. However, the financial factor is not only a social problem, but also one concerning the individual. Some recommended drugs are not covered by the healthcare system but need to be covered by the patients themselves. These are expenses for OTC medications and copayments for prescribed medications. Hence, with the rising number of drugs, costs for patients are rising as well.

A feared consequence of pDDIs that can make them so dangerous is the altered efficacy of one or both drugs interacting, thereby provoking treatment failure [23]. This could be life-threatening to the patient [46]. A change in the drug's effect and effectiveness can be triggered by another drug by influencing the patient's metabolism pharmacokinetically and/or pharmacodynamically. Moreover, the drug's toxicity could be altered and dangerously increased, or new side effects resulting from the combination of two or more drugs might appear. As an example, one of the most frequently recorded pDDIs in our cohort with a frequency of 3.3% was the interaction between acetylsalicylic acid and enoxaparin. The severity of this pDDI was rated as moderate because of an insignificantly increased bleeding risk due to this combination [47]. Such combination side effects that can cause new complaints may even result in the prescription of additional drugs, leading to a prescribing cascade [48].

By reducing the number of drugs used, PP rates as well as the number of pDDIs will also decrease. To achieve this, there are several approaches for doctors and healthcare providers, including pharmacists. The simplest one is to deprescribe any unnecessary medication and to stop prescribing new medication that may not be necessary. Unnecessary medications can be those that do not contribute significantly to the patients' health, that have the same active agents as one of the other drugs the patient is taking or even OTC drugs that are more likely to do harm than good. Another way is to regularly check each patient's medication, for example, in the form of a "brown bag review" [49], which has been found to be well-working [50]. Following this approach, the patient is asked to bring all drugs currently being taken, including self-bought OTC drugs and nutritional or herbal supplements. This might give the doctor a better overview of what the patient is actually taking—especially supplements and OTC drugs, which are otherwise often not considered [51,52]. Another similar approach is called medication therapy management (MTM), a service provided by participating pharmacies that was implemented by the American Pharmacists Association and several national pharmacy groups from the US. MTM includes a wide range of services such as medication therapy review, a personal medication record and a medication-related action plan, aiming at improving therapeutic outcomes and reducing drug-related problems [53]. Studies have found MTM to improve clinical outcomes, medication adherence and appropriateness [54,55]. It also entails economic advantages by reducing healthcare costs [56]. These results show that a national implementation of this kind of service in local pharmacies could reduce the number of drugs taken, and therefore the number of pDDIs and the number of inpatient admissions. Approaches such as this one should be emphasized. In general, the role of pharmacists as the experts for medication should not be forgotten, as they are an important link between doctors and patients. It has been shown that pharmacists' interventions can be an effective factor in identifying and managing pDDIs, as they can intervene on different levels [57], for example, by contacting the prescriber and discussing critical drug combinations or new prescriptions, by changing the dosage or formulation of a drug after consulting the doctor or by advising the patient and giving instructions on how to prevent and detect pDDIs (i.e., more frequent blood glucose monitoring at home). Of course, this does not only apply to Rx medications but also to OTCs and dietary supplements, for which counseling might be even more important, as doctors mostly inform their patients less about these

than compared with Rx drugs. Another outstanding advantage pharmacists usually have is the overview of all prescriptions even from different specialist doctors, whereas doctors mostly only see the drugs they are prescribing. For all of this, a trustful patient–pharmacist relationship is important [58], which can therefore be a limiting factor: if a patient does not have one pharmacy of trust, but uses several pharmacies at the same time, it might be more difficult to build a relationship to one pharmacist and the advantage of a medication schedule overview becomes lost, resulting in a less adequate consultation.

Furthermore, when prescribing a new drug, doctors should always check for pDDIs with the current medication. In addition, the connection between doctors and pharmacists should be strengthened, so that doctors can consult pharmacists more regularly to discuss patients' medication schedule and pharmacists can advise doctors about, for example, newly approved drugs. Further, regular checkups with CDSS should be carried out as they are updated occasionally. Hence, doctors should make it a routine to check each patient's medication plan (for example, once a year). Pharmacists should always give advice about possible complications and ask for existing medication to check for possible interactions when handing out new substances (Rx as well as OTC drugs). Another important factor is treatment adherence, which also ought to be checked regularly. If patients do not take their medication properly, doctors may be tempted to prescribe new medications because therapeutic effects are not apparent. Another way to interrupt possible prescribing cascades is to provide a medication plan for each patient, where all their drugs are listed with indication and dosage. This gives a better overview for the patient as well as for other doctors the patient is seeing. This is especially true since, in a disease with a "thousand different faces", doctors from different disciplines may be involved in the treatment of the patient with MS. By knowing what other drugs the patient is taking, doctors can pursue possible causes of side effects that they might otherwise mistakenly consider as separate illnesses. For example, if a patient is taking opioid analgesics, their doctor would know that possible constipation is not an independent symptom but a side effect of the established medication [44]. There are many more approaches to reduce the risk of PP and of possibly dangerous DDIs [59,60].

With an average age of 48.6 years, our cohort was similar to two large national MS cohorts with a mean age of 49 years [61] and 46 years [62], respectively. The same holds for the mean age at disease onset. According to the atlas of MS, mean age at MS onset in Germany is 33 years [4], while in our cohort, it was at 35 years (Table 1). The sex ratio in our study cohort of around 2.4 to 1 (female vs. male) was also highly similar to that reported in other studies [61,63,64]. Our data on PP and pDDIs are thus based on a representative study population of 627 patients with CIS/MS in total.

Nevertheless, there are limitations of our study. As it is a cross-sectional study, no causal relationships can be derived. However, several associations could be clearly shown. These should be studied in more detail in longitudinal studies. Moreover, as the data acquisition was performed by conducting patient interviews, an underestimation of the number of drugs taken by the patients is possible, especially with regard to the use of OTC drugs and nutritional supplements. Studies have found discrepancies regarding patient-reported medication plans and medical records: up to 60% of patients had at least one omission error in what they reported to take [65], which means that they did not report at least one drug that they used before hospital admission, where the interview took place. The rate of falsely reported drugs is particularly high for the medication group of nonsteroid anti-inflammatory drugs (NSAIDs) [65,66]. Especially for OTC NSAIDs, such as ibuprofen or diclofenac, omission errors are frequent [66]. Therefore, we presume unreported drugs and therefore undetected pDDIs in our data. The same applies to compliance and adherence, as we do not know if the patients really took their medication properly as prescribed. Further, metabolism is different in each patient, and many of the interactions that were detected in the CDSS and DDID are dependent on, e.g., dosage, metabolic factors, application form and timing of the concurrently taken drugs. As many pDDIs are mediated through induction or inhibition of cytochrome P450 (CYP) enzymes,

interindividual differences in the expression of these enzymes make it difficult to predict a patient's reaction to drugs [67,68]. For this reason, we are referring to *potential* DDIs. It cannot be concluded that any of these are guaranteed to apply, but there is always the possibility that the pDDI will actually occur. What should be further investigated is the question whether patients actually know about the risk of pDDIs and whether they are informed by their doctors about warning signs and symptoms of pDDIs.

It should be noted that every CDSS or DDID has a different definition of, for example, a "mild" interaction and the classification of pDDI severities is difficult in general. Moreover, each CDSS/DDID also has some limitations. In *MediQ*, some substances, especially nutritional supplements and homeopathics, were not available, such as vitamin K2 or canephron. Conversely, in *Stockley's*, the information was not as precise as in *MediQ* at some points, as for example, different hormonal substances were summarized under the term "oral contraceptives", no matter which estrogens or gestagens were entered.

5. Conclusions

To conclude, we found that 53.3% of the studied patients with MS had total PP. For 63.8% of our patients, we detected at least one pDDI. The majority (65.4%) of all recorded pDDIs was rated as mild. pDDIs occurred significantly more often in patients with total PP (93.4%) and patients with Rx PP (97.1%) than in those without PP. This underlines that PP is a significant predictor of pDDIs [69]. Comorbidities were related to the occurrence of at least one pDDI: significantly higher pDDI prevalence rates were found for patients with cardiovascular, neurological, psychiatric and orthopedic comorbidities. Although only a small percentage (1.1%) of patients had a severe pDDI, representing a direct threat to the patients, the overall number of pDDIs was surprisingly high. Our study shows that there is a need for more awareness of PP and pDDIs. Doctors in general, but especially those treating chronically ill patients such as those with MS, should pay special attention to pDDIs. The use of CDSS/DDID to detect pDDIs may help avoiding them and should be integrated in physicians' daily routines. Doctors should be informed about their patients' OTC drug use and include these OTC drugs in their evaluation of pDDIs. Future studies should focus on PP and pDDIs in middle-aged patients and further uncover possible dangers in patient healthcare that can be avoided.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/pharmaceutics14030592/s1>, Table S1: Groups of comorbidities present in MS patients with and without polypharmacy, Table S2: Prevalence of pDDIs in MS patients stratified by different comorbidity groups, Table S3: All pDDIs of all patients with MS.

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Data Availability Statement: The data supporting the findings of this study are available in the article and/or Supplementary Materials. Readers are welcome to contact the corresponding author by e-mail to request access to the raw de-identified data used in this work.

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References

- Masnoon, N.; Shakib, S.; Kalisch-Ellett, L.; Caughey, G.E. What is polypharmacy? A systematic review of definitions. *BMC Geriatr.* **2017**, *17*, 230. [CrossRef]
- Frahm, N.; Hecker, M.; Zettl, U.K. Polypharmacy among patients with multiple sclerosis: A qualitative systematic review. *Expert Opin. Drug Saf.* **2020**, *19*, 139–145. [CrossRef] [PubMed]
- Payne, R.A. The epidemiology of polypharmacy. *Clin. Med.* **2016**, *16*, 465–469. [CrossRef]
- Walton, C.; King, R.; Rechtman, L.; Kaye, W.; Leray, E.; Marrie, R.A.; Robertson, N.; La Rocca, N.; Uitdehaag, B.; van der Mei, I.; et al. Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition. *Mult. Scler. Houndmills Basingstoke Engl.* **2020**, *26*, 1816–1821. [CrossRef]
- Filippi, M.; Bar-Or, A.; Piehl, F.; Preziosa, P.; Solari, A.; Vukusic, S.; Rocca, M.A. Multiple sclerosis. *Nat. Rev. Dis. Primer* **2018**, *4*, 43. [CrossRef] [PubMed]
- Rommer, P.S.; Eichstädt, K.; Ellenberger, D.; Flachenecker, P.; Friede, T.; Haas, J.; Kleinschnitz, C.; Pöhlau, D.; Rienhoff, O.; Stahmann, A.; et al. Symptomatology and symptomatic treatment in multiple sclerosis: Results from a nationwide MS registry. *Mult. Scler. Houndmills Basingstoke Engl.* **2019**, *25*, 1641–1652. [CrossRef]
- Selmi, C.; Mix, E.; Zettl, U.K. A clear look at the neuroimmunology of multiple sclerosis and beyond. *Autoimmun. Rev.* **2012**, *11*, 159–162. [CrossRef] [PubMed]
- Ellenberger, D.; Flachenecker, P.; Haas, J.; Hellwig, K.; Paul, F.; Stahmann, A.; Warnke, C.; Zettl, U.K.; Rommer, P.S.; Scientific Advisory Group by the German MS-Register of the German MS Society. Is benign MS really benign? What a meaningful classification beyond the EDSS must take into consideration. *Mult. Scler. Relat. Disord.* **2020**, *46*, 102485. [CrossRef] [PubMed]
- Ellenberger, D.; Flachenecker, P.; Fneish, F.; Frahm, N.; Hellwig, K.; Paul, F.; Stahmann, A.; Warnke, C.; Rommer, P.S.; Zettl, U.K. Aggressive multiple sclerosis: A matter of measurement and timing. *Brain J. Neurol.* **2020**, *143*, e97. [CrossRef]
- Lublin, F.D.; Reingold, S.C.; Cohen, J.A.; Cutter, G.R.; Sorensen, P.S.; Thompson, A.J.; Wolinsky, J.S.; Balcer, L.J.; Banwell, B.; Barkhof, F.; et al. Defining the clinical course of multiple sclerosis: The 2013 revisions. *Neurology* **2014**, *83*, 278–286. [CrossRef]
- Thompson, A.J.; Banwell, B.L.; Barkhof, F.; Carroll, W.M.; Coetzee, T.; Comi, G.; Correale, J.; Fazekas, F.; Filippi, M.; Freedman, M.S.; et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol.* **2018**, *17*, 162–173. [CrossRef]
- Hauser, S.L.; Cree, B.A.C. Treatment of Multiple Sclerosis: A Review. *Am. J. Med.* **2020**, *133*, 1380–1390.e2. [CrossRef] [PubMed]
- Rommer, P.S.; Zettl, U.K. Managing the side effects of multiple sclerosis therapy: Pharmacotherapy options for patients. *Expert Opin. Pharmacother.* **2018**, *19*, 483–498. [CrossRef] [PubMed]
- Moiola, L.; Rommer, P.S.; Zettl, U.K. Prevention and management of adverse effects of disease modifying treatments in multiple sclerosis. *Curr. Opin. Neurol.* **2020**, *33*, 286–294. [CrossRef]
- Rommer, P.; Zettl, U.K. Treatment options in Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorders. *Curr. Pharm. Des.* **2022**, *28*, 428–436. [CrossRef]
- Wiendl, H.; Gold, R.; Berger, T.; Derfuss, T.; Linker, R.; Mäurer, M.; Aktas, O.; Baum, K.; Berghoff, M.; Bittner, S.; et al. Multiple Sclerosis Therapy Consensus Group (MSTCG): Position statement on disease-modifying therapies for multiple sclerosis (white paper). *Ther. Adv. Neurol. Disord.* **2021**, *14*, 17562864211039648. [CrossRef]
- Hemmer, B. *Diagnose und Therapie der Multiplen Sklerose, Neuromyelitis-Optica-Spektrum-Erkrankungen und MOG-IgG-assoziierten Erkrankungen; Leitlinien für Diagnostik und Therapie in der Neurologie; Deutsche Gesellschaft für Neurologie (Hrsg.): Berlin, Germany, 2021; Available online: www.dgn.org/leitlinien (accessed on 13 October 2021).*
- Schiess, N.; Calabresi, P. Multiple Sclerosis. *Semin. Neurol.* **2016**, *36*, 350–356. [CrossRef]
- Frahm, N.; Hecker, M.; Zettl, U.K. Polypharmacy in Chronic Neurological Diseases: Multiple Sclerosis, Dementia and Parkinson's Disease. *Curr. Pharm. Des.* **2021**, *27*, 4008–4016. [CrossRef]
- Niu, J.; Straubinger, R.M.; Mager, D.E. Pharmacodynamic Drug-Drug Interactions. *Clin. Pharmacol. Ther.* **2019**, *105*, 1395–1406. [CrossRef]
- Moura, C.S.; Acurcio, F.A.; Belo, N.O. Drug-drug interactions associated with length of stay and cost of hospitalization. *J. Pharm. Pharm. Sci. Publ. Can. Soc. Pharm. Sci. Soc. Can. Sci. Pharm.* **2009**, *12*, 266–272. [CrossRef]
- Rekić, D.; Reynolds, K.S.; Zhao, P.; Zhang, L.; Yoshida, K.; Sachar, M.; Piquette Miller, M.; Huang, S.-M.; Zineh, I. Clinical Drug-Drug Interaction Evaluations to Inform Drug Use and Enable Drug Access. *J. Pharm. Sci.* **2017**, *106*, 2214–2218. [CrossRef]

23. Köhler, G.I.; Bode-Böger, S.M.; Busse, R.; Hoopmann, M.; Welte, T.; Böger, R.H. Drug-drug interactions in medical patients: Effects of in-hospital treatment and relation to multiple drug use. *Int. J. Clin. Pharmacol. Ther.* **2000**, *38*, 504–513. [CrossRef] [PubMed]
24. Dechanont, S.; Maphanta, S.; Butthum, B.; Kongkaew, C. Hospital admissions/visits associated with drug-drug interactions: A systematic review and meta-analysis. *Pharmacoepidemiol. Drug Saf.* **2014**, *23*, 489–497. [CrossRef]
25. Kurtzke, J.F. Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). *Neurology* **1983**, *33*, 1444–1452. [CrossRef]
26. Moss, B.P.; Rensel, M.R.; Hersh, C.M. Wellness and the Role of Comorbidities in Multiple Sclerosis. *Neurother. J. Am. Soc. Exp. Neurother.* **2017**, *14*, 999–1017. [CrossRef] [PubMed]
27. Marrie, R.A.; Cohen, J.; Stuve, O.; Trojano, M.; Sørensen, P.S.; Reingold, S.; Cutter, G.; Reider, N. A systematic review of the incidence and prevalence of comorbidity in multiple sclerosis: Overview. *Mult. Scler. Houndmills Basingstoke Engl.* **2015**, *21*, 263–281. [CrossRef] [PubMed]
28. mediQ-Startseite. Available online: <https://www.mediq.ch/> (accessed on 13 October 2021).
29. Hahn, M.; Roll, S.C. Validation of interaction databases in psychopharmacotherapy. *Der Nervenarzt* **2018**, *89*, 319–326. [CrossRef]
30. Digital Medicines Information Suite. Available online: <https://about.medicinescomplete.com/> (accessed on 13 October 2021).
31. Frahm, N.; Hecker, M.; Langhorst, S.E.; Mashhadiakbar, P.; Haker, M.-C.; Zettl, U.K. The risk of polypharmacy, comorbidities and drug–drug interactions in women of childbearing age with multiple sclerosis. *Ther. Adv. Neurol. Disord.* **2020**, *13*, 1756286420969501. [CrossRef]
32. Rodrigues, M.C.S.; de Oliveira, C. Drug-drug interactions and adverse drug reactions in polypharmacy among older adults: An integrative review. *Rev. Lat. Am. De Enferm.* **2016**, *24*, e2800. [CrossRef]
33. Astorp, J.; Gjela, M.; Jensen, P.; Bak, R.D.; Gazerani, P. Patterns and characteristics of polypharmacy among elderly residents in Danish nursing homes. *Future Sci. OA* **2020**, *6*, FSO590. [CrossRef]
34. Merlo, J.; Liedholm, H.; Lindblad, U.; Björck-Linné, A.; Fält, J.; Lindberg, G.; Melander, A. Prescriptions with potential drug interactions dispensed at Swedish pharmacies in January 1999: Cross sectional study. *BMJ* **2001**, *323*, 427–428. [CrossRef] [PubMed]
35. Bogetti-Salazar, M.; González-González, C.; Juárez-Cedillo, T.; Sánchez-García, S.; Rosas-Carrasco, O. Severe potential drug-drug interactions in older adults with dementia and associated factors. *Clinics* **2016**, *71*, 17–21. [CrossRef]
36. Dookeeram, D.; Bidaisee, S.; Paul, J.F.; Nunes, P.; Robertson, P.; Maharaj, V.R.; Sammy, I. Polypharmacy and potential drug-drug interactions in emergency department patients in the Caribbean. *Int. J. Clin. Pharm.* **2017**, *39*, 1119–1127. [CrossRef]
37. Medication Safety in Polypharmacy: Technical Report. Available online: <https://www.who.int/publications-detail-redirect/medication-safety-in-polypharmacy-technical-report> (accessed on 17 October 2021).
38. Soler, O.; Barreto, J.O.M. Community-Level Pharmaceutical Interventions to Reduce the Risks of Polypharmacy in the Elderly: Overview of Systematic Reviews and Economic Evaluations. *Front. Pharmacol.* **2019**, *10*, 302. [CrossRef]
39. Hanlon, J.T.; Pieper, C.F.; Hajjar, E.R.; Sloane, R.J.; Lindblad, C.I.; Ruby, C.M.; Schmadier, K.E. Incidence and predictors of all and preventable adverse drug reactions in frail elderly persons after hospital stay. *J. Gerontol. A Biol. Sci. Med. Sci.* **2006**, *61*, 511–515. [CrossRef] [PubMed]
40. Maher, R.L.; Hanlon, J.; Hajjar, E.R. Clinical consequences of polypharmacy in elderly. *Expert Opin. Drug Saf.* **2014**, *13*, 57–65. [CrossRef]
41. Klauer, T.; Zettl, U.K. Compliance, adherence, and the treatment of multiple sclerosis. *J. Neurol.* **2008**, *255 Suppl 6*, 87–92. [CrossRef]
42. Zettl, U.K.; Bauer-Steinhusen, U.; Glaser, T.; Hechenbichler, K.; Limmroth, V.; Study Group. Evaluation of an electronic diary for improvement of adherence to interferon beta-1b in patients with multiple sclerosis: Design and baseline results of an observational cohort study. *BMC Neurol.* **2013**, *13*, 117. [CrossRef]
43. Gaeta, T.J.; Fiorini, M.; Ender, K.; Bove, J.; Diaz, J. Potential drug-drug interactions in elderly patients presenting with syncope. *J. Emerg. Med.* **2002**, *22*, 159–162. [CrossRef]
44. Rambhade, S.; Chakarborty, A.; Shrivastava, A.; Patil, U.K.; Rambhade, A. A survey on polypharmacy and use of inappropriate medications. *Toxicol. Int.* **2012**, *19*, 68–73. [CrossRef]
45. Hovstadius, B.; Åstrand, B.; Persson, U.; Petersson, G. Acquisition cost of dispensed drugs in individuals with multiple medications—a register-based study in Sweden. *Health Policy Amst. Neth.* **2011**, *101*, 153–161. [CrossRef] [PubMed]
46. Zhang, C.; Shen, L.; Cui, M.; Liu, X.; Gu, Z. Ticagrelor-induced life-threatening bleeding via the cyclosporine-mediated drug interaction: A case report. *Medicine* **2017**, *96*, e8065. [CrossRef] [PubMed]
47. Eriksson, B.I.; Rosencher, N.; Friedman, R.J.; Homering, M.; Dahl, O.E. Concomitant use of medication with antiplatelet effects in patients receiving either rivaroxaban or enoxaparin after total hip or knee arthroplasty. *Thromb. Res.* **2012**, *130*, 147–151. [CrossRef] [PubMed]
48. Rochon, P.A.; Gurwitz, J.H. The prescribing cascade revisited. *Lancet Lond. Engl.* **2017**, *389*, 1778–1780. [CrossRef]
49. Sarzynski, E.M.; Luz, C.C.; Rios-Bedoya, C.F.; Zhou, S. Considerations for using the “brown bag” strategy to reconcile medications during routine outpatient office visits. *Qual. Prim. Care* **2014**, *22*, 177–187.
50. Nathan, A.; Goodyer, L.; Lovejoy, A.; Rashid, A. “Brown bag” medication reviews as a means of optimizing patients’ use of medication and of identifying potential clinical problems. *Fam. Pract.* **1999**, *16*, 278–282. [CrossRef] [PubMed]

51. Floor-Schreuderling, A.; Heringa, M.; Buurma, H.; Bouvy, M.L.; De Smet, P.A.G.M. Missed drug therapy alerts as a consequence of incomplete electronic patient records in Dutch community pharmacies. *Ann. Pharmacother.* **2013**, *47*, 1272–1279. [[CrossRef](#)]
52. Olesen, C.; Harbig, P.; Barat, I.; Damsgaard, E.M. Absence of “over-the-counter” medicinal products in on-line prescription records: A risk factor of overlooking interactions in the elderly. *Pharmacoepidemiol. Drug Saf.* **2013**, *22*, 145–150. [[CrossRef](#)]
53. American Pharmacists Association. National Association of Chain Drug Stores Foundation Medication therapy management in pharmacy practice: Core elements of an MTM service model (version 2.0). *J. Am. Pharm. Assoc.* **2008**, *48*, 341–353. [[CrossRef](#)]
54. Viswanathan, M.; Kahwati, L.C.; Golin, C.E.; Blalock, S.J.; Coker-Schwimmer, E.; Posey, R.; Lohr, K.N. Medication therapy management interventions in outpatient settings: A systematic review and meta-analysis. *JAMA Intern. Med.* **2015**, *175*, 76–87. [[CrossRef](#)]
55. Tsuyuki, R.T.; Johnson, J.A.; Teo, K.K.; Simpson, S.H.; Ackman, M.L.; Biggs, R.S.; Cave, A.; Chang, W.-C.; Dzavik, V.; Farris, K.B.; et al. A randomized trial of the effect of community pharmacist intervention on cholesterol risk management: The Study of Cardiovascular Risk Intervention by Pharmacists (SCRIP). *Arch. Intern. Med.* **2002**, *162*, 1149–1155. [[CrossRef](#)] [[PubMed](#)]
56. Isetts, B.J.; Schondelmeyer, S.W.; Artz, M.B.; Lenarz, L.A.; Heaton, A.H.; Wadd, W.B.; Brown, L.M.; Cipolle, R.J. Clinical and economic outcomes of medication therapy management services: The Minnesota experience. *J. Am. Pharm. Assoc.* **2008**, *48*, 203–214. [[CrossRef](#)] [[PubMed](#)]
57. Aghili, M.; Kasturirangan, M.N. Management of Drug–Drug Interactions among Critically Ill Patients with Chronic Kidney Disease: Impact of Clinical Pharmacist’s Interventions. *Indian J. Crit. Care Med. Peer-Rev. Off. Publ. Indian Soc. Crit. Care Med.* **2021**, *25*, 1226–1231. [[CrossRef](#)] [[PubMed](#)]
58. McCullough, M.B.; Petrakis, B.A.; Gillespie, C.; Solomon, J.L.; Park, A.M.; Ourth, H.; Morreale, A.; Rose, A.J. Knowing the Patient: A Qualitative Study on Care-Taking and the Clinical Pharmacist–Patient Relationship. *Res. Soc. Adm. Pharm.* **2016**, *12*, 78–90. [[CrossRef](#)] [[PubMed](#)]
59. Coe, A.; Kaylor-Hughes, C.; Fletcher, S.; Murray, E.; Gunn, J. Deprescribing intervention activities mapped to guiding principles for use in general practice: A scoping review. *BMJ Open* **2021**, *11*, e052547. [[CrossRef](#)]
60. Carpenter, M.; Berry, H.; Pelletier, A.L. Clinically Relevant Drug–Drug Interactions in Primary Care. *Am. Fam. Physician* **2019**, *99*, 558–564.
61. Weih, M.; Roßnagel, F.; Dikow, H.; Wehrle, K.; Braune, S.; Bergmann, A. Data on multiple sclerosis in Germany and their representation in the ambulatory registry NeuroTransData (NTD) network. *Fortschr. Neurol. Psychiatr.* **2020**, *88*, 379–385. [[CrossRef](#)]
62. Flachenecker, P.; Eichstädt, K.; Berger, K.; Ellenberger, D.; Friede, T.; Haas, J.; Kleinschnitz, C.; Pöhlau, D.; Rienhoff, O.; Stahmann, A.; et al. Multiple sclerosis in Germany: Updated analysis of the German MS Registry 2014–2018. *Fortschr. Neurol. Psychiatr.* **2020**, *88*, 436–450. [[CrossRef](#)]
63. Boström, I.; Stawiarz, L.; Landtblom, A.-M. Sex ratio of multiple sclerosis in the National Swedish MS Register (SMSreg). *Mult. Scler. Houndmills Basingstoke Engl.* **2013**, *19*, 46–52. [[CrossRef](#)]
64. Ohle, L.-M.; Ellenberger, D.; Flachenecker, P.; Friede, T.; Haas, J.; Hellwig, K.; Parciak, T.; Warnke, C.; Paul, F.; Zettl, U.K.; et al. Chances and challenges of a long-term data repository in multiple sclerosis: 20th birthday of the German MS registry. *Sci. Rep.* **2021**, *11*, 13340. [[CrossRef](#)]
65. Tam, V.C.; Knowles, S.R.; Cornish, P.L.; Fine, N.; Marchesano, R.; Etchells, E.E. Frequency, type and clinical importance of medication history errors at admission to hospital: A systematic review. *CMAJ Can. Med. Assoc. J. J. Assoc. Médicale Can.* **2005**, *173*, 510–515. [[CrossRef](#)]
66. Abdolrasulnia, M.; Weichold, N.; Shewchuk, R.; Saag, K.; Cobaugh, D.J.; LaCivita, C.; Weissman, N.; Allison, J. Agreement between medical record documentation and patient-reported use of nonsteroidal antiinflammatory drugs. *Am. J. Health Syst. Pharm.* **2006**, *63*, 744–747. [[CrossRef](#)]
67. Palleria, C.; Di Paolo, A.; Giofrè, C.; Caglioti, C.; Leuzzi, G.; Siniscalchi, A.; De Sarro, G.; Gallelli, L. Pharmacokinetic drug–drug interaction and their implication in clinical management. *J. Res. Med. Sci. Off. J. Isfahan Univ. Med. Sci.* **2013**, *18*, 601–610.
68. Zanger, U.M.; Schwab, M. Cytochrome P450 enzymes in drug metabolism: Regulation of gene expression, enzyme activities, and impact of genetic variation. *Pharmacol. Ther.* **2013**, *138*, 103–141. [[CrossRef](#)] [[PubMed](#)]
69. Obreli Neto, P.R.; Nobili, A.; de Lyra, D.P.; Pilger, D.; Guidoni, C.M.; de Oliveira Baldoni, A.; Cruciol-Souza, J.M.; de Carvalho Freitas, A.L.; Tettamanti, M.; Gaeti, W.P.; et al. Incidence and predictors of adverse drug reactions caused by drug–drug interactions in elderly outpatients: A prospective cohort study. *J. Pharm. Pharm. Sci.* **2012**, *15*, 332–343. [[CrossRef](#)] [[PubMed](#)]

8.2. Publikation 2

Associated factors of potential drug-drug interactions and drug-food interactions in patients with multiple sclerosis


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Associated factors of potential drug–drug interactions and drug–food interactions in patients with multiple sclerosis

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Abstract

Background: Multiple sclerosis (MS) is the most common immune-mediated demyelinating disease in younger adults. Patients with MS (PwMS) are vulnerable to the presence of potential drug–drug interactions (pDDIs) and potential drug–food interactions (pDFIs) as they take numerous medications to treat MS, associated symptoms and comorbidities. Knowledge about pDDIs and pDFIs can increase treatment success and reduce side effects.

Objective: We aimed at determining the frequency and severity of pDDIs and pDFIs in PwMS, with regard to polypharmacy.

Methods: In the cross-sectional study, we analysed pDDIs and pDFIs of 627 PwMS aged ≥ 18 years. Data collection was performed through patient record reviews, clinical examinations and structured patient interviews. pDDIs and pDFIs were identified using two DDI databases: *Drugs.com Interactions Checker* and *Stockley's Interactions Checker*.

Results: We identified 2587 pDDIs (counted with repetitions). Of 627 PwMS, 408 (65.1%) had ≥ 1 pDDI. Polypharmacy (concomitant use of ≥ 5 drugs) was found for 334 patients (53.3%). Patients with polypharmacy (Pw/P) were found to have a 15-fold higher likelihood of having ≥ 1 severe pDDI compared with patients without polypharmacy (Pw/oP) (OR: 14.920, $p < 0.001$). The most frequently recorded severe pDDI was between citalopram and fingolimod. Regarding pDFIs, ibuprofen and alcohol was the most frequent severe pDFI.

Conclusion: Pw/P were particularly at risk of severe pDDIs. Age and educational level were found to be factors associated with the occurrence of pDDIs, independent of the number of medications taken. Screening for pDDIs/pDFIs should be routinely done by the clinical physician to increase drug safety and reduce side effects.

Keywords: multiple sclerosis, over-the-counter drugs, polypharmacy, potential drug–drug interactions, potential drug–food interactions

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Introduction

Potential drug–drug interactions (pDDIs) occur when the pharmacodynamics or pharmacokinetics of an active substance are affected by the intake of other drugs. Changes in drug metabolism such as induction or inhibition of CYP enzymes may be observed due to pDDIs. As a result, pDDIs lead to adverse drug effects that may have serious consequences for the patients.

It is estimated that 200,000 to 1 million patients are seriously affected by pDDIs each year in Germany alone.¹ The number of aged and multimorbid patients is increasing rapidly, and consequently, the number of prescribed medications, leading to an exponential increase in the number of pDDIs.¹ Older age typically implies taking a greater number of medications prescribed by different healthcare providers, which increases the

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risk for clinically relevant pDDIs.² pDDIs are responsible for 1–5% of hospitalisations.³ Moura *et al.*⁴ focused on the economic and clinical problems and they demonstrated that pDDIs are associated with prolonged hospitalisations (15 *versus* 8 days) as well as additional costs to the health care system (US\$192 or more per hospitalisation). In a US study, the burden of pDDIs on the health care system was reported to be between \$30 and \$180 billion annually.^{5,6} As a leading cause of increased morbidity and mortality, 770,000 deaths per year can be attributed to pDDIs, which contribute to about 20% of all reported adverse drug events.⁷

Potential drug–food interactions (pDFIs) are another cause of adverse drug reactions. Food can regulate the metabolism of drugs, for example, *via* CYP enzymes and lead to altered drug levels, resulting in increased or decreased drug effects. To improve therapeutic outcomes, it is important for pharmacists and prescribing physicians to identify efficacy-influencing food, ingredients beverages and dietary/lifestyle habits.⁸

Multiple sclerosis (MS) is an immune-mediated demyelinating disease of the central nervous system associated with inflammation and degeneration.⁹ Worldwide, over 2 million people are affected by MS, with an increasing trend (1990 *versus* 2016: + 10.4%).^{10,11} MS can occur in different disease courses: primary progressive MS (PPMS), relapsing-remitting MS (RRMS) or secondary progressive MS (SPMS). A clinically isolated syndrome (CIS) often characterises the initial stage of the disease.^{12,13} As a multifaceted disease, MS can cause a variety of symptoms such as spasticity, bladder dysfunction, visual problems or cognitive and psychological changes.¹⁴ The drug therapy of MS is divided into relapse therapy, disease-modifying therapy and medication for symptom reduction (e.g. antispasmodics like baclofen or cannabinoids).^{15–18} Disease-modifying drugs (DMDs) are used for immunomodulating treatment.^{19–21} This is supplemented by symptomatic therapies and comorbidity drugs.^{14,22} To maintain quality of life and improve functional outcomes, many patients seek additional help in the use of complementary and alternative medicines (CAM) such as dietary supplements or herbal drugs.^{23–25} It was reported that 67% to 80% of MS patients use CAM and half of them even as an alternative to conventional therapies.^{26,27} For example, vitamin D supplementation is often part of a nutritional health plan because

low cholecalciferol levels in serum have been associated with a higher risk of relapses.²⁸

The combined use of DMDs, symptomatic therapeutics, comorbidity drugs and CAM increases the risk of polypharmacy.^{29,30} According to the most common definition, polypharmacy means taking five or more drugs.³¹ In a systematic review of seven studies, we found a polypharmacy rate of 15–59% in patients with MS.³² In a previous study, we also analysed pDDIs in a cohort of women of childbearing age with MS ($N=131$). Clinically relevant pDDIs were six times more frequent in women with polypharmacy than in women without polypharmacy.³³

In the present study, we captured the full spectrum of pDDIs in a large cohort of patients with MS. By identifying frequently interacting drugs and common pDDIs, we aimed to raise awareness of avoidable drug combinations and potentially serious consequences, especially in patients affected by polypharmacy. We also evaluated the severity of pDFIs to assess their clinical relevance and provide recommendations for optimising pharmacotherapy in MS.

Materials and methods

Study population

The data for this cross-sectional study were collected from March 2017 to May 2020 at the neurological department (neuroimmunology section) of the Rostock University Medical Centre and at the neurological department of the Ecumenical Hainich Hospital Mühlhausen (Germany). Patients younger than 18 years and subjects without the diagnosis of MS or CIS according to the revised McDonald criteria were excluded.³⁴ For data collection, we asked inpatients during their hospital stay and outpatients in the waiting period before their routine examination to voluntarily participate in our study. With informed written consent, we acquired data from a total of 627 participants. This study thus included more patients than our previous study on MS ($n=131$) and comparable studies on the analysis of pDDIs in other disease contexts (up to $n=481$).^{33,35–38} Approval for this study was granted by the ethics committees of the Thuringia Medical Association and the Rostock University Medical Centre (approval numbers A 2014-0089 and A 2019-0048). The study was conducted in accordance with the Declaration of Helsinki.

Data acquisition

Clinical, pharmaceutical and sociodemographic data of the included patients were collected based on a structured interview, supplemented by anamnesis, a review of patient records and a clinical examination. We considered prescription drugs (Rx), over-the-counter drugs (OTC), dietary supplements (e.g. vitamins and minerals) and CAM in order not to miss any drug intake outside the doctor's 'radar'.

The data were divided into three categories:

1. Sociodemographic data: We obtained data on age, sex, partnership, employment status, school years (without training or university studies), level of education, number of children and siblings as well as place of residence (<5000 residents: rural community, 5000–19,999: provincial town, 20,000–99,999: medium-sized town, $\geq 100,000$: city).
2. Clinical data: This category comprised disease duration, disease course (CIS, RRMS, PPMS or SPMS), the number and types of comorbidities and the degree of disability according to the Expanded Disability Status Scale (EDSS).³⁹
3. Pharmaceutical data: The data collected included all medications taken per patient with the corresponding names of active ingredients, the trade names of the drugs, the types of application and dosages.

Classification of drugs

The medicines were divided into three categories:

1. Therapy goal: We distinguished DMDs, symptomatic drugs and comorbidity drugs. DMDs are immunomodulatory drugs for the therapy of MS. Methylprednisolone was included as DMD because it was used for relapse therapy or as repeated pulse therapy for progressive courses. Symptomatic drugs are used to relieve the various symptoms of MS. Comorbidity drugs are medications to treat comorbidities not related to MS.
2. Period of drug intake: We differentiated between long-term drugs (taken daily or at regular intervals) and on-demand drugs (*pro re nata*, PRN) which are used sporadically or acutely.
3. Access: We distinguished drugs that are available only as OTC or on prescription (Rx). OTC drugs also include preparations

that are sold in small doses without a prescription, but require a prescription in higher doses (e.g. ibuprofen).

Following the most frequently used definition, polypharmacy was present if five or more medications were taken by the patient.³¹

Identification of drug–drug and drug–food interactions

For the determination of pDDIs and pDFIs, we used two online drug interaction databases: *Drugs.com Drug Interactions Checker* and *Stockley's Interactions Checker*. The database search was performed from May 2020 to October 2020 using either the trade names or the active ingredients of the drugs as appropriate.

Drugs.com is a free online database, which provides information on more than 24,000 prescription and OTC medicines as well as herbal pharmaceuticals for patients and medical professionals. In *Drugs.com*, pDDIs are distinguished according to three levels of severity: major (highly clinically significant), moderate (moderately clinically significant) and minor (minimally clinically significant).

Stockley's Interactions Checker, maintained by the Royal Pharmaceutical Society, is a subscription-based tool for identifying pDDIs. It contains over 85,000 interactions and is aimed at healthcare professionals. It provides drug interactions with food, beverages and smoking as well as interactions between drugs and herbs. *Stockley's Interactions Checker* also classifies the severity of pDDIs into three groups: severe (high clinical relevance), moderate (moderate clinical relevance) and minor (minimal clinical relevance).

Summary score of pDDI and pDFI severity

To combine the information on pDDI severity from *Drugs.com* and *Stockley's*, we assigned scores to each severity level: zero points (no evidence of interaction), one point (minor/mild), two points (moderate) and three points (major/severe). For each pDDI, the sum of the scores of the two databases was then used to define five degrees of pDDI severity (mild, mild-moderate, moderate, moderate-severe and severe). In the case of pDFIs, we adhered to the three-level severity rating from mild to severe, while discrepancies in the information from *Drugs.com* and *Stockley's* were

resolved by considering only the higher pDFI severity rating in further analyses.

Statistical analysis

For the statistical analysis of the data, we used IBM SPSS Statistics 27.0 and R version 3.6.0. Descriptive statistics of sociodemographic, clinical and pharmaceutical data as well as pDDI and pDFI data were obtained as means (\pm standard deviation), medians, ranges, frequencies and percentages. For comparing patients with polypharmacy (Pw/P) and patients without polypharmacy (Pw/oP), we used the following statistical tests: Fisher's exact test, chi-square test, Mann-Whitney *U* test and two-sample two-tailed *t* test as appropriate. The significance level was set at $\alpha = 0.05$. Binary logistic regression analyses were performed to evaluate the association of sociodemographic, clinical and pharmaceutical data with the presence of at least one pDDI or at least one moderate-severe/severe pDDI. To determine the combined effect of those variables on the occurrence of at least one pDDI, we used multiple logistic regression analysis with forward selection based on likelihood ratio statistics. The figures were created with Microsoft Office Professional Plus 2016, R package corrplot and Cytoscape version 3.9.0.

Results

Characterisation of the study population

In our cohort of 627 patients, the mean age [\pm standard deviation (SD)] was 48.6 (\pm 13.3) years, and the proportion of female patients was 70.3%. The median EDSS score was 3.5 and the median disease duration was 10 years. Regarding disease course, 415 patients (66.2%) had CIS/RRMS, followed by 154 patients (24.6%) with SPMS and 58 patients (9.3%) with PPMS. Seven patients did not take any medication. The other 620 patients with CIS/MS took 3341 medications in total (counted with repetitions). The median number of medications taken was five. The patients were six times more likely to take long-term medications than on-demand medications (4.6 drugs *versus* 0.8 drugs on average). On average, 4.2 Rx drugs were taken, compared with an average of 1.1 OTC drugs. Regarding the treatment goal, 82.8% of the MS patients took DMDs. A mean of 2.0 drugs were taken for symptom reduction and an average of 2.5 drugs were taken to treat comorbidities (Table 1).

Comparison of patients with and without polypharmacy

There were 334 patients (53.3%) with polypharmacy (Pw/P) and 293 (46.7%) patients without polypharmacy (Pw/oP). Pw/P were on average 9.4 years older than Pw/oP ($p < 0.001$, *t* test). The median EDSS score was 4.5 for Pw/P and 2.0 for Pw/oP. The median disease duration was 3.5 years longer for Pw/P than for Pw/oP. Comorbidities were present in 83.8% of Pw/P compared with 46.8% of Pw/oP ($p < 0.001$, Mann-Whitney *U* tests) (Supplementary Table 1).

pDDIs

We recorded 2587 pDDIs in the data set (counted with repetitions, 1211 different pDDIs without repetitions, Supplementary Table 2). The majority of pDDIs were mild (57.1%). Moderate-severe and severe interactions together accounted for slightly more than 10% of all pDDIs (9.5% and 3.4%, respectively) (Figure 1).

In the total population, 408 patients (65.1%) had at least one pDDI. In contrast, we detected no pDDI for 219 patients (34.9%). The patients with pDDIs were on average 9 years older and had a 3 years longer disease duration than the patients without pDDIs. Patients without pDDIs had a median EDSS score of 2.0 whereas patients with at least one pDDI had a median EDSS score of 4.0. The median number of medications taken was 6 in patients with at least one pDDI and 2 in patients without pDDIs. In patients without pDDIs, CIS/RRMS was by far the most common course of MS (87.7% of patients), whereas in patients with at least one pDDI, SPMS and PPMS also accounted for large proportions (CIS/RRMS: 54.7%, SPMS: 33.3%; PPMS: 12.0%) (Table 1). The median number of pDDIs was 4 for Pw/P and 0 for Pw/oP ($p < 0.001$, Mann-Whitney *U* test) (Supplementary Table 1). There were 73 patients (11.6%) taking at least 10 drugs (excessive polypharmacy). For those, the median number of pDDIs was 15 (range: 2–55) and 32.9% of them had at least one severe pDDI.

When comparing the prevalence of pDDIs (independently of pDDI severity) Pw/P had clearly more often ≥ 1 pDDI as compared with Pw/oP (93.1% *versus* 33.1%) (Figure 2).

Table 1. Sociodemographic, clinical and pharmaceutical data of MS patients with and without pDDIs.

Parameter	All patients (N=627)		Patients with ≥ 1 pDDI (N=408)		Patients with no pDDI (N=219)		p-value
Sociodemographic data							
Sex							0.927 ^a
Female	441 (70.3%)		286 (70.1%)		155 (70.8%)		
Male	186 (29.7%)		122 (29.9%)		64 (29.2%)		
Age (years)	19–86 ^b	48.6 (13.3) ^c	21–86 ^b	51.9 (12.6) ^c	19–75 ^b	42.5 (12.5) ^c	<0.001 ^d
School years	6–18 ^b	10.5 (1.3) ^c	6–18 ^b	10.3 (1.2) ^c	8–14 ^b	10.8 (1.3) ^c	<0.001 ^d
Educational level							<0.001 ^e
No training	19 (3.0%)		12 (2.9%)		7 (3.2%)		
Skilled worker	398 (63.5%)		280 (68.6%)		118 (53.9%)		
Technical college	89 (14.2%)		56 (13.7%)		33 (15.1%)		
University	121 (19.3%)		60 (14.7%)		61 (27.9%)		
Employment status							<0.001 ^e
In training	7 (1.1%)		2 (0.5%)		5 (2.3%)		
In studies	6 (1.0%)		1 (0.2%)		5 (2.3%)		
Employed	269 (42.9%)		130 (31.9%)		139 (63.5%)		
Unemployed	25 (4.0%)		13 (3.2%)		12 (5.5%)		
Retired	304 (48.5%)		253 (62.0%)		51 (23.3%)		
Others	16 (2.6%)		9 (2.2%)		7 (3.2%)		
Partnership							0.702 ^a
No	162 (25.8%)		103 (25.2%)		59 (26.9%)		
Yes	465 (74.2%)		305 (74.8%)		160 (73.1%)		
Place of residence							0.040 ^e
Rural community	224 (35.7%)		150 (36.8%)		74 (33.8%)		
Provincial town	108 (17.2%)		77 (18.9%)		31 (14.2%)		
Medium-sized town	112 (17.9%)		77 (18.9%)		35 (16.0%)		
City	183 (29.3%)		104 (25.5%)		79 (36.1%)		
Number of children	0–4 ^b	1 ^f	0–4 ^b	1 ^f	0–4 ^b	1 ^f	0.003 ^g
0	169 (27.0%)		91 (22.3%)		78 (35.6%)		
1	170 (27.1%)		118 (28.9%)		52 (23.7%)		
≥ 2	288 (45.9%)		199 (48.8%)		89 (40.6%)		
Number of siblings	0–13 ^b	1 ^f	0–13 ^b	1 ^f	0–11 ^b	1 ^f	0.035 ^g
0	71 (11.3%)		40 (9.8%)		31 (14.2%)		
1	305 (48.6%)		194 (47.5%)		111 (50.7%)		
≥ 2	251 (40.0%)		174 (42.6%)		77 (35.2%)		
Clinical data							
EDSS score	0–9.0 ^b	3.5 ^f	0–9.0 ^b	4.0 ^f	0–7.5 ^b	2.0 ^f	<0.001 ^g

(Continued)

Table 1. (Continued)

Parameter	All patients (N=627)		Patients with ≥ 1 pDDI (N=408)		Patients with no pDDI (N=219)		p-value
Disease duration (years)	0–52 ^b	10 ^f	0–50 ^b	12 ^f	0–52 ^b	9 ^f	<0.001 ^g
Disease course							<0.001 ^e
CIS/RRMS	415 (66.2%)		223 (54.7%)		192 (87.7%)		
SPMS	154 (24.6%)		136 (33.3%)		18 (8.2%)		
PPMS	58 (9.3%)		49 (12.0%)		9 (4.1%)		
Comorbidities	0–9 ^b	1 ^f	0–9 ^b	1 ^f	0–7 ^b	0 ^f	<0.001 ^g
No	184 (29.3%)		68 (16.7%)		116 (53.0%)		
Yes	443 (70.7%)		340 (83.3%)		103 (47.0%)		
Polypharmacy							<0.001 ^a
No	293 (46.7%)		97 (23.8%)		196 (89.5%)		
Yes	334 (53.3%)		311 (76.2%)		23 (10.5%)		
Pharmaceutical data							
Number of drugs taken	0–19 ^b	5 ^f	2–19 ^b	6 ^f	0–9 ^b	2 ^f	<0.001 ^g
0	7 (1.1%)		0 (0.0%)		7 (3.2%)		
1–4	286 (45.6%)		97 (23.8%)		189 (86.3%)		
5–9	261 (41.6%)		238 (58.3%)		23 (10.5%)		
≥ 10	73 (11.6%)		73 (17.9%)		0 (0.0%)		
Drugs divided by							
Period of drug intake							
Long-term drugs	0–16 ^b	4.6 (3.1) ^h	1–16 ^b	5.8 (3.0) ^h	0–9 ^b	2.2 (1.5) ^h	<0.001 ^g
PRN drugs	0–7 ^b	0.8 (1.2) ^h	0–7 ^b	1.0 (1.3) ^h	0–5 ^b	0.4 (0.8) ^h	<0.001 ^g
Access							
Rx drugs	0–18 ^b	4.2 (3.0) ^h	1–18 ^b	5.4 (3.0) ^h	0–6 ^b	1.9 (1.2) ^h	<0.001 ^g
OTC drugs	0–8 ^b	1.1 (1.3) ^h	0–8 ^b	1.4 (1.3) ^h	0–7 ^b	0.7 (1.1) ^h	<0.001 ^g
Therapy goal							
DMDs	0–2 ^b	0.9 (0.4) ^h	0–2 ^b	0.9 (0.4) ^h	0–1 ^b	0.7 (0.4) ^h	<0.001 ^g
Symptomatic drugs	0–9 ^b	2.0 (2.0) ^h	0–9 ^b	2.6 (2.0) ^h	0–8 ^b	0.8 (1.1) ^h	<0.001 ^g
Comorbidity drugs	0–14 ^b	2.5 (2.4) ^h	0–14 ^b	3.3 (2.6) ^h	0–6 ^b	1.0 (1.1) ^h	<0.001 ^g

p-value for comparing patients with and without pDDIs (significant differences are indicated in bold). CIS, clinically isolated syndrome; DMD, disease-modifying drug; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; N, number of patients; OTC, over-the-counter; pDDI, potential drug–drug interaction; PPMS, primary progressive MS; PRN, *pro re nata*; RRMS, relapsing–remitting MS; Rx, prescription; SPMS, secondary progressive MS.

^aFisher's exact test.

^bRange.

^cMean value (standard deviation).

^dTwo-sample two-tailed *t* test.

^eChi-squared test.

^fMedian.

^gMann–Whitney *U* test.

^hAverage number of drugs taken per patient (standard deviation).

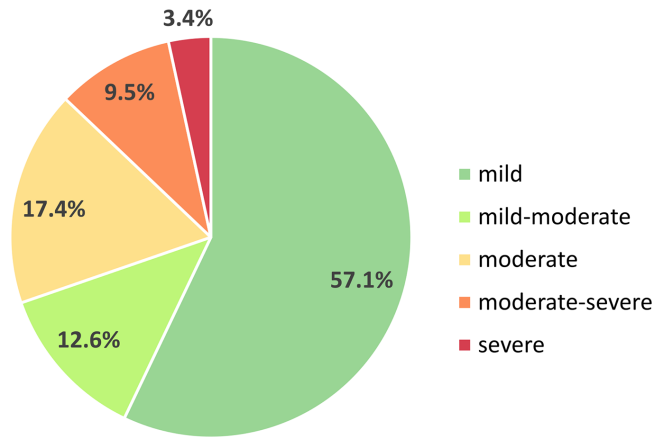


Figure 1. Percentage distribution of severity of drug–drug interactions in patients with MS. In this study, 627 MS patients had a total number of 2587 pDDIs. This chart shows the frequencies of the five pDDI severity levels. Most pDDIs were mild (57.1%), while moderate pDDIs had a share of 17.4%. Moderate-severe or severe interactions accounted for 12.9% of all interactions. MS, multiple sclerosis; pDDIs, potential drug–drug interactions.

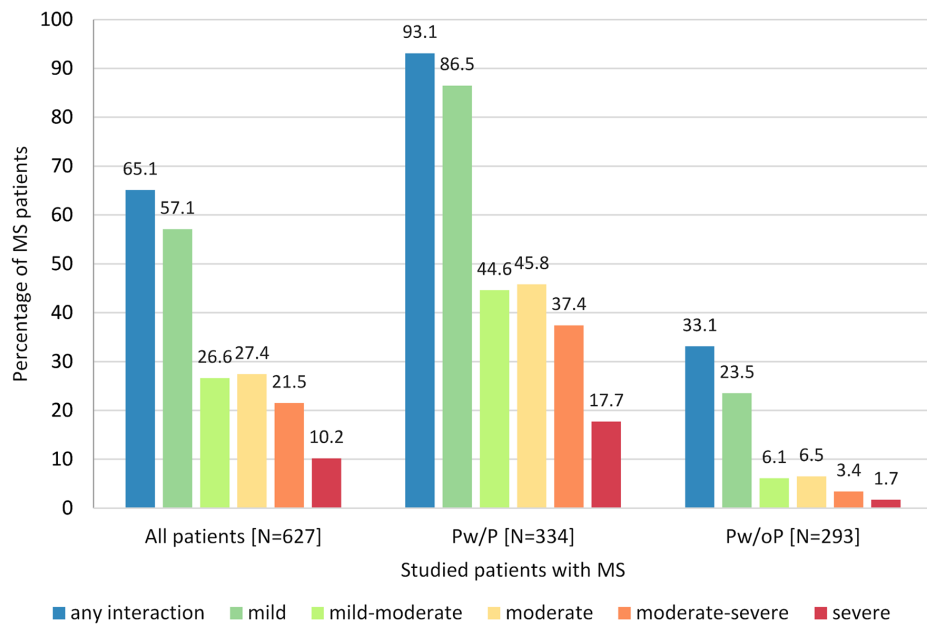


Figure 2. Comparison of the prevalence of pDDIs of different severity degrees between MS patients with and without polypharmacy. The proportion of patients having pDDIs was significantly higher in Pw/P versus Pw/oP for each degree of severity (Fisher’s exact test $p < 0.001$). Pw/P were three times more likely to have ≥ 1 pDDI than Pw/oP (93.1% versus 33.1%). The distribution of the severity degrees was skewed towards more severe interactions in Pw/P as compared with Pw/oP (chi-square test $p = 0.001$). Pw/P had a roughly 10-fold higher risk of severe interactions. pDDIs were determined using *Stockley’s Interactions Checker* and *Drugs.com Interactions Checker*. Note that the patients could have several pDDIs of different severities at the same time. MS, multiple sclerosis; pDDIs, potential drug–drug interactions; Pw/oP, patients without polypharmacy; Pw/P, patients with polypharmacy.

Associations of sociodemographic, clinical and pharmaceutical data with the occurrence of pDDIs

Independent associations were found between the following sociodemographic variables and the presence of at least one pDDI: age, school years, educational level, place of residence as well as the number of children and siblings. Older patients with MS were more likely to have one or more pDDIs than younger patients (OR: 1.060 for each one-year increase, 95% CI: 1.045–1.075). More years spent in school were associated with a lower likelihood of having at least one pDDI (OR: 0.771, 95% CI: 0.676–0.879). Further associations with the occurrence of pDDIs in patients with MS were found for degree of disability (EDSS score), disease duration and number of comorbidities ($p < 0.001$). A one-point increase in the EDSS score led to a 58.6% increase in the probability of having at least one pDDI (OR: 1.586, 95% CI: 1.434–1.754). The odds for the occurrence of at least one pDDI rose with increasing years of disease duration (OR: 1.041, 95% CI: 1.021–1.061) and even doubled with each additional comorbidity (OR: 2.235, 95% CI: 1.893–2.638). Polypharmacy increased the likelihood for the occurrence of pDDIs by 27-fold (OR: 27.322, 95% CI: 16.764–44.529) (Table 2). Multiple logistic regression analysis revealed four associated variables: age (OR: 1.034), educational level (OR: 0.502), number of drugs taken (OR: 2.608) and number of DMDs used (OR: 2.105). The final model had a prediction accuracy of 85.8%. Similar associations were found with regard to the occurrence of moderate-severe/severe pDDIs. Notably, the risk of moderate-severe or severe pDDIs was increased 15-fold with polypharmacy (OR: 14.920, 95% CI: 8.363–26.619) (Table 2).

Interacting active ingredients

The top 20 agents, for which the most pDDIs were counted, ranged from methylprednisolone (pDDI count: 247) to calcium (pDDI count: 73) (Table 3). About 20% of all patients took at least one of these top 20 agents: pantoprazole ($N = 178$ patients, 28.4%), enoxaparin ($N = 127$ patients, 20.3%) and methylprednisolone ($N = 123$ patients, 19.6%). There were significant differences in the use of drugs between patients with and without polypharmacy. For instance, enoxaparin was more often taken by Pw/P than by Pw/oP (Pw/P: 34.1% versus Pw/oP: 4.4%) ($p < 0.001$,

Fisher's exact test). A listing of all agents involved in pDDIs with the number of total interactions and the distribution of pDDI severity levels is provided in Supplementary Table 3.

All moderate-severe ($N = 18$) or severe ($N = 5$) pDDIs that occurred in at least three of the MS patients studied are shown in Table 4. The most relevant severe pDDIs were found between the following drugs: citalopram \leftrightarrow fingolimod ($N = 7$ patients) and acetylsalicylic acid \leftrightarrow ibuprofen ($N = 6$ patients). The moderate-severe pDDIs acetylsalicylic acid \leftrightarrow enoxaparin, ibuprofen \leftrightarrow enoxaparin, methylprednisolone \leftrightarrow ibuprofen, enoxaparin \leftrightarrow ramipril and citalopram \leftrightarrow ibuprofen were significantly more often recorded in Pw/P than in Pw/oP ($p < 0.05$, Fisher's exact tests). For those agents involved in the 23 moderate-severe or severe pDDIs that were repeatedly observed and that are listed in Table 4, we visualised the frequency and severity of all pairwise interactions in Figure 3. Among these, the most frequent pDDI was found between interferon beta-1a and ibuprofen ($N = 29$ patients).

Potential drug–food interactions

In the analysis of pDFIs, 254 drugs were found to be involved in pDFIs in our study population. Of these, 34 drugs belong to at least one severe pDFI, with alcohol being responsible for 21 severe pDFIs (e.g. acetaminophen \leftrightarrow alcohol) (Supplementary Table 4). The pDFIs with the 20 active ingredients most frequently involved in pDDIs are listed in Table 5 and visualised in Figure 4. The only severe pDFI in this subset was found for ibuprofen \leftrightarrow alcohol. A total of 105 patients (16.7%) may be at risk of this pDFI as they took ibuprofen. Three pDFIs were found for dronabinol, which may affect 47 patients (7.5%) (Table 5).

Discussion

This study focused on the prevalence and severity of pDDIs in patients with MS. Therefore, the medication schedules of 627 patients were checked. Our study serves the purpose of showing health professionals which patients may have a high likelihood of having pDDIs and which drugs may be most frequently involved. A special feature of this study represents the analysis of pDFIs of the drugs that were taken by our patient cohort.

Table 2. Association of sociodemographic, clinical and pharmaceutical parameters with the presence of pDDIs or moderate-severe/severe pDDIs.

Parameter	≥1 pDDI (all severities)			≥1 moderate-severe/severe pDDI		
	OR	95% confidence interval	p-value ^a	OR	95% confidence interval	p-value ^a
Sociodemographic data						
Sex (ref. women)	1.033	(0.721–1.481)	0.859	0.938	(0.630–1.396)	0.751
Age (in years)	1.060	(1.045–1.075)	<0.001	1.071	(1.053–1.089)	<0.001
School years (in years)	0.771	(0.676–0.879)	<0.001	0.641	(0.540–0.760)	<0.001
Educational level (ref. no. training)	0.680	(0.560–0.827)	<0.001	0.678	(0.534–0.862)	0.001
Partnership (ref. single)	1.092	(0.752–1.585)	0.644	0.825	(0.551–1.236)	0.351
Place of residence (ref. rural area)	0.871	(0.763–0.995)	0.041	0.959	(0.829–1.109)	0.572
Number of children (number)	1.259	(1.064–1.489)	0.007	1.430	(1.191–1.718)	<0.001
Number of siblings (number)	1.149	(1.016–1.301)	0.027	1.259	(1.122–1.413)	<0.001
Clinical data						
EDSS score (points)	1.586	(1.434–1.754)	<0.001	1.479	(1.346–1.626)	<0.001
Disease duration (in years)	1.041	(1.021–1.061)	<0.001	1.048	(1.029–1.068)	<0.001
Comorbidities (number)	2.235	(1.893–2.638)	<0.001	1.811	(1.595–2.056)	<0.001
Pharmaceutical data						
Number of drugs taken (number)	2.665	(2.271–3.127)	<0.001	1.616	(1.487–1.756)	<0.001
Polypharmacy (ref. no. polypharmacy)	27.322	(16.764–44.529)	<0.001	14.920	(8.363–26.619)	<0.001
Long-term drugs (number)	2.306	(2.006–2.652)	<0.001	1.576	(1.453–1.710)	<0.001
PRN drugs (number)	1.884	(1.523–2.332)	<0.001	1.482	(1.276–1.722)	<0.001
Rx drugs (number)	2.665	(2.260–3.143)	<0.001	1.755	(1.594–1.932)	<0.001
OTC drugs (number)	1.743	(1.463–2.076)	<0.001	1.145	(0.999–1.311)	0.052
DMD (number)	2.504	(1.673–3.748)	<0.001	1.324	(0.836–2.097)	0.232
Symptomatic drugs (number)	2.221	(1.900–2.595)	<0.001	1.360	(1.241–1.491)	<0.001
Comorbidity drugs (number)	2.187	(1.876–2.550)	<0.001	1.831	(1.642–2.043)	<0.001

ORs and significance values were calculated by binary logistic regression analysis for each parameter. The analysis was based on the data of 627 patients with MS. In the left part of the table, 408 patients with pDDIs were compared with 219 patients without pDDIs. In the right part of the table, 157 patients with ≥1 moderate-severe or severe pDDI were compared with 470 patients without such pDDI. DMD, disease-modifying drug; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; OR, odds ratio; OTC, over-the-counter; pDDI, potential drug–drug interaction; PRN, *pro re nata*; ref., reference; Rx, prescription.

^a*p*: *p*-value for each regression coefficient (*p* < 0.05 are indicated in bold).

Table 3. The top 20 substances for which the most pDDIs were identified in the cohort of MS patients (N = 627).

Active ingredient	pDDI count	Degree of pDDI severity, N					Patients, N (%)			P ^a	
		Mild		Moderate		Severe	Total (N = 627)		Pw/P (N = 334)		Pw/oP (N = 293)
		Mild-severe	Moderate-severe	Moderate	Severe		Total	%			
Methylprednisolone	247	106	51	63	22	5	123 (19.6%)	110 (32.9%)	13 (4.4%)	<0.001	
Acetylsalicylic acid	232	83	37	72	33	7	55 (8.8%)	48 (14.4%)	7 (2.4%)	<0.001	
Ibuprofen	211	87	37	28	53	6	105 (16.7%)	61 (18.3%)	44 (15.0%)	0.286	
Pantoprazole	190	122	6	61	0	1	178 (28.4%)	155 (46.4%)	23 (7.8%)	<0.001	
Baclofen	189	107	17	58	7	0	78 (12.4%)	72 (21.6%)	6 (2.0%)	<0.001	
Ramipril	164	80	7	41	31	5	53 (8.5%)	41 (12.3%)	12 (4.1%)	<0.001	
Bisoprolol	151	95	30	18	8	0	51 (8.1%)	46 (13.8%)	5 (1.7%)	<0.001	
Cannabidiol	139	121	3	14	1	0	46 (7.3%)	40 (12.0%)	6 (2.0%)	<0.001	
Dronabinol	136	120	5	6	5	0	47 (7.5%)	41 (12.3%)	6 (2.0%)	<0.001	
Torsemide	127	60	10	54	3	0	22 (3.5%)	22 (6.6%)	0 (0.0%)	<0.001	
Citalopram	122	36	32	11	16	27	33 (5.3%)	25 (7.5%)	8 (2.7%)	0.011	
Enoxaparin	112	33	0	6	71	2	127 (20.3%)	114 (34.1%)	13 (4.4%)	<0.001	
Hydrochlorothiazide	94	42	5	39	6	2	8 (1.3%)	7 (2.1%)	1 (0.3%)	0.073	
Metoprolol	90	53	17	18	2	0	29 (4.6%)	25 (7.5%)	4 (1.4%)	<0.001	
Levothyroxine	90	47	3	37	3	0	82 (13.1%)	55 (16.5%)	27 (9.2%)	0.009	
Amlodipine	86	40	18	25	3	0	25 (4.0%)	22 (6.6%)	3 (1.0%)	<0.001	
Duloxetine	84	63	3	5	10	3	21 (3.3%)	19 (5.7%)	2 (0.7%)	<0.001	
Zopiclone	83	70	1	10	0	2	65 (10.4%)	58 (17.4%)	7 (2.4%)	<0.001	
Magnesium	79	76	3	0	0	0	65 (10.4%)	49 (14.7%)	16 (5.5%)	<0.001	
Calcium	73	63	0	9	1	0	33 (5.3%)	32 (9.6%)	1 (0.3%)	<0.001	

The table is sorted by the total number of pDDIs per drug in the data set (pDDI count). In addition, the number of pDDIs broken down by degree of severity and the number of MS patients who received the respective drugs are provided. MS, multiple sclerosis; N, number of patients; pDDI, potential drug-drug interaction; Pw/P, patients with polypharmacy; Pw/oP, patients without polypharmacy.
^ap-value according to Fisher's exact test for comparing Pw/P and Pw/oP (significant differences are indicated in bold).

Table 4. Moderate-severe and severe pDDIs that were recorded in at least three patients with MS.

Potential drug–drug interaction	All patients (N=627)	Pw/P (N=334)	Pw/oP (N=293)	p ^a
Severe				
Citalopram ↔ Fingolimod	7 (1.1%)	5 (1.5%)	2 (0.7%)	0.458
Acetylsalicylic acid ↔ Ibuprofen	6 (1.0%)	6 (1.8%)	0 (0.0%)	0.033
Citalopram ↔ Solifenacin	5 (0.8%)	4 (1.2%)	1 (0.3%)	0.378
Ciprofloxacin ↔ Methylprednisolone	3 (0.5%)	3 (0.9%)	0 (0.0%)	0.252
Escitalopram ↔ Fingolimod	3 (0.5%)	2 (0.6%)	1 (0.3%)	1.000
Moderate-severe				
Acetylsalicylic acid ↔ Enoxaparin	21 (3.3%)	20 (6.0%)	1 (0.3%)	<0.001
Enoxaparin ↔ Ibuprofen	16 (2.6%)	14 (4.2%)	2 (0.7%)	0.005
Ibuprofen ↔ Methylprednisolone	14 (2.2%)	13 (3.9%)	1 (0.3%)	0.002
Enoxaparin ↔ Ramipril	13 (2.1%)	13 (3.9%)	0 (0.0%)	<0.001
Interferon beta-1a ↔ Ramipril	7 (1.1%)	5 (1.5%)	2 (0.7%)	0.458
Citalopram ↔ Ibuprofen	6 (1.0%)	6 (1.8%)	0 (0.0%)	0.033
Diclofenac ↔ Enoxaparin	4 (0.6%)	4 (1.2%)	0 (0.0%)	0.127
Diclofenac ↔ Methylprednisolone	4 (0.6%)	4 (1.2%)	0 (0.0%)	0.127
Acetylsalicylic acid ↔ Duloxetine	4 (0.6%)	4 (1.2%)	0 (0.0%)	0.127
Ramipril ↔ Tizanidine	4 (0.6%)	4 (1.2%)	0 (0.0%)	0.127
Candesartan ↔ Tizanidine	4 (0.6%)	4 (1.2%)	0 (0.0%)	0.127
Acetylsalicylic acid ↔ Venlafaxine	3 (0.5%)	2 (0.6%)	1 (0.3%)	1.000
Enoxaparin ↔ Valsartan	3 (0.5%)	3 (0.9%)	0 (0.0%)	0.252
Baclofen ↔ Levodopa	3 (0.5%)	3 (0.9%)	0 (0.0%)	0.252
Duloxetine ↔ Ibuprofen	3 (0.5%)	2 (0.6%)	1 (0.3%)	1.000
Insulin glargine ↔ Ramipril	3 (0.5%)	3 (0.9%)	0 (0.0%)	0.252
Citalopram ↔ Dronabinol	3 (0.5%)	3 (0.9%)	0 (0.0%)	0.252
Escitalopram ↔ Ibuprofen	3 (0.5%)	3 (0.9%)	0 (0.0%)	0.252

The table is sorted by pDDI severity and prevalence. It is also indicated how often a particular pDDI was counted in the groups of patients with polypharmacy (Pw/P) and without polypharmacy (Pw/oP), respectively. MS, multiple sclerosis; N, number of patients; pDDIs, potential drug–drug interactions; Pw/oP, patients without polypharmacy; Pw/P, patients with polypharmacy.

^ap: p-value according to Fisher's exact test for comparing Pw/P and Pw/oP (significant differences are indicated in bold).

Our previous studies are, to our knowledge, the only studies on pDDIs in patients with MS in the literature.^{33,40} We found in a smaller study of 131 women in childbearing age that the prevalence of

having at least one pDDI of average danger was significantly higher in Pw/P than in Pw/oP (31.5% versus 5.2%, $p < 0.001$).³³ There were also significant associations between polypharmacy and

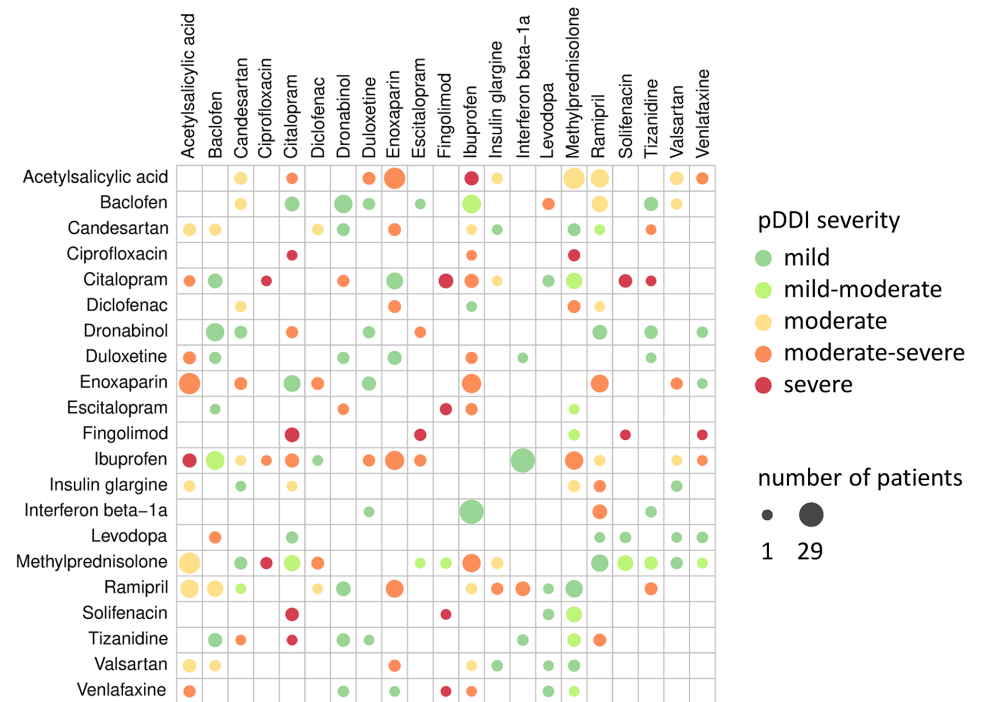


Figure 3. Interaction heatmap of drugs for which moderate-severe or severe pDDIs have been repeatedly noted in patients with MS. Shown is the frequency and severity of pDDIs between drugs involved in moderate-severe or severe pDDIs that were identified in at least three patients with MS (see also Table 4). The active ingredients are listed in alphabetical order. The size of the dots represents the frequency of pDDIs in the patient cohort ($N=627$). The colour of the dots indicates the severity of the pDDI. The most common interaction has been recorded between interferon beta-1a and ibuprofen [29 patients]. MS, multiple sclerosis; pDDIs, potential drug-drug interactions.

higher age, higher degree of disability (EDSS score) and higher number of comorbidities.³³ In our recently published study, we found significantly higher pDDI prevalence rates for MS patients with cardiovascular, neurological, psychiatric and orthopaedic comorbidities.⁴⁰ The present study focused on the analysis of pDDIs and their severity by incorporating information from Drugs.com. We determined sociodemographic and clinical factors that are associated with an increased likelihood of (severe) pDDIs in patients with MS.

The relatively high proportion of MS patients with at least one pDDI detected in our study is a main consequence of the drug-intensive treatment to reduce disease activity and to alleviate MS-related symptoms but is also related to the

presence of comorbidities, especially older age. However, only slightly more than 10% of all recorded pDDIs were moderate-severe or severe pDDIs. Due to the lack of studies on pDDIs in MS patients, we looked at the prevalence of pDDIs in other medical disciplines. Doan *et al.*³⁷ demonstrated that the likelihood of at least one pDDI in hospitalised patients aged 65 or older depends on the number of drugs taken (e.g. 50% for persons taking 5–9 drugs). In a study of outpatients taking oral anticancer drugs, a proportion of 263 patients (89.4%) had at least one pDDI.³⁸ Ismail *et al.* reported an overall prevalence of pDDIs of 78% in 678 patients receiving chemotherapy. A large proportion of those (39.2%) had only one to two pDDIs, and severe interactions accounted for the majority of pDDIs (67.3%).⁴¹ However, the results are difficult to

Table 5. Drug–food interactions for the top 20 substances for which the most pDDIs were identified.

Active ingredient	Patients, N (%)	Degree of drug–food interaction severity		
		Mild	Moderate	Severe
Methylprednisolone	123 (19.6%)	–	Grapefruit, tobacco	–
Acetylsalicylic acid	55 (8.8%)	Alcohol, food	–	–
Ibuprofen	105 (16.7%)	–	–	Alcohol
Pantoprazole	178 (28.4%)	–	–	–
Baclofen	78 (12.4%)	–	Alcohol	–
Ramipril	53 (8.5%)	Alcohol	Food (potassium-containing)	–
Bisoprolol	51 (8.1%)	Alcohol, tobacco	–	–
Cannabidiol	46 (7.3%)	–	Food (high-fat meal), grapefruit	–
Dronabinol	47 (7.5%)	Grapefruit	Alcohol, food (high-fat meal)	–
Torasemide	22 (3.5%)	–	–	–
Citalopram	33 (5.3%)	–	Alcohol	–
Enoxaparin	127 (20.3%)	–	–	–
Hydrochlorothiazide	8 (1.3%)	–	–	–
Metoprolol	29 (4.6%)	Alcohol, tobacco	Food	–
Levothyroxine	82 (13.1%)	–	Food ^a , grapefruit	–
Amlodipine	25 (4.0%)	Grapefruit	Alcohol	–
Duloxetine	21 (3.3%)	Tobacco	Alcohol	–
Zopiclone	65 (10.4%)	–	Alcohol, food (high-fat/heavy meal)	–
Magnesium	65 (10.4%)	–	–	–
Calcium	33 (5.3%)	–	Food ^b	–

pDFI databases often only indicate 'food' as an interaction partner of a drug. This usually refers to the timing of the food intake or a certain food composition such as food high in fat or potassium-containing food. Food: The timing of food intake is a factor influencing the absorption of ingested medicines. Patients, N (%): number of MS patients who have received the respective drug. pDDIs, potential drug–drug interactions; pDFI, potential drug–food interaction.

^aDietary fibre, milk, soy products, coffee, nuts and seeds.

^bFoods high in oxalic acid (e.g. spinach or rhubarb) or phytic acid (e.g. bran and whole grains).

compare because different patient inclusion criteria and different pDDI databases were used in these studies.

Although the association between polypharmacy and pDDIs is well known, our study described for the first time that polypharmacy led to a 15-fold (OR: 14.920) increase in the likelihood of severe or moderate–severe pDDIs in patients with MS. In our study, we found an age difference between

patients with and without pDDIs of almost 10 years. The association between the occurrence of pDDIs and age is consistent with previous studies. Janchawee *et al.*⁴² found that the odds of having at least one pDDI increased with an age difference of 20 years by a factor of 1.8. Bjerrum *et al.*² could also relate the presence of pDDIs to higher age and a higher number of medications taken. The increase in multimorbidity with age and the use of multiple medications to treat

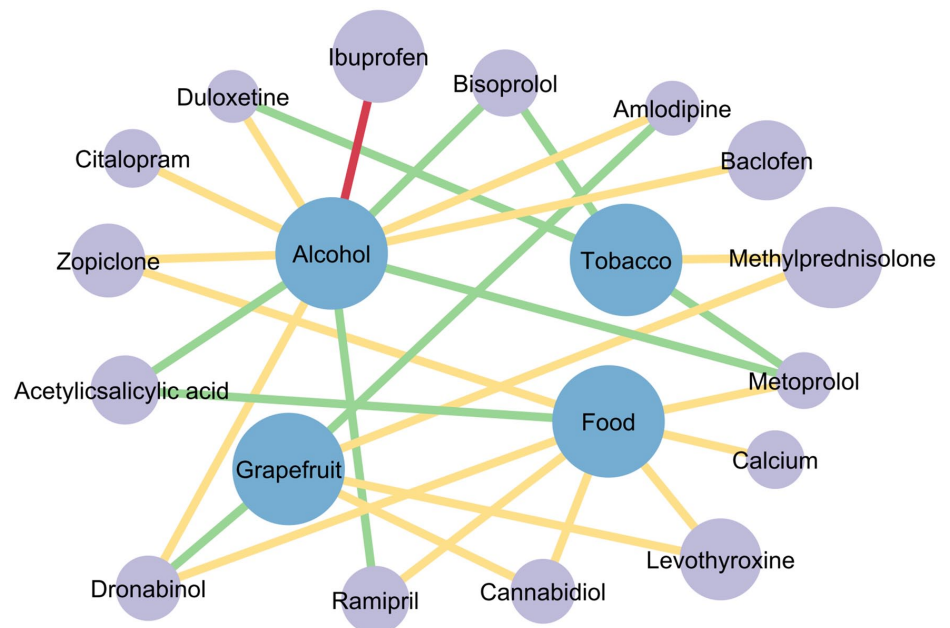


Figure 4. Network of pDFIs for the top 20 drugs for which the most pDDIs were recorded. Grey dots stand for medications and blue dots represent other substances. The size of the grey dots shows the number of patients taking this drug (e.g. methylprednisolone was taken by 123 patients). The line colour indicates the severity of the interaction: green – mild interaction, yellow – moderate interaction and red – severe interaction. A total of 28 pDFIs were found between the top 20 drugs for which the most pDDIs were identified (Tables 3 and 5). Between those, there are 100 different pDDIs, which are not shown here for simplicity. A severe pDFI was found between ibuprofen and alcohol. Among the top 20 drugs, pantoprazole, torasemide, enoxaparin, hydrochlorothiazide and magnesium showed no interaction with alcohol, food or tobacco smoke. pDDIs, potential drug–drug interactions; pDFIs, potential drug–food interactions.

comorbidities significantly contribute to polypharmacy and the risk of pDDIs.

Methylprednisolone was the active substance with the most interactions in our data set (247 pDDIs). Of these, most pDDIs were mild interactions ($n=106$). On the one hand, relapse therapy with high-dose methylprednisolone is carried out as standard.⁴³ On the other hand repeated pulse therapy (e.g. every 3 months) is also occasional used by patients with SPMS or PPMS, although convincing class I evidence is lacking.⁴⁴ During the period of our data collection, many patients with PPMS or SPMS have been treated in this way.^{45,46} Acetylsalicylic acid and ibuprofen ranked second and third among the agents with the highest pDDI counts. This puts two common OTC agents among the top triggers of pDDIs in patients with MS. Ibuprofen, as a non-steroidal

anti-inflammatory drug (NSAID), influences inflammatory processes, acts as an analgesic and is one of the therapeutic strategies for treatment-related pain.⁴⁷ For instance, the early phase of interferon beta therapy can lead to flu-like symptoms and myalgias, while ibuprofen (as well as acetaminophen) can help to relieve these.^{48–50} Of note, only a few pDDIs were recorded for vitamin supplements (vitamin C, D and E), and none of them were moderate-severe or severe.

Particularly severe pDDIs are clinically relevant due to their potentially serious consequences (including death). The most frequent moderate-severe pDDIs were acetylsalicylic acid \leftrightarrow enoxaparin ($N=21$ patients, 3.3%) and enoxaparin \leftrightarrow ibuprofen ($N=16$, 2.6%). Those pDDIs may lead to an increased risk of bleeding. For this reason, careful clinical laboratory monitoring is indicated

in patients taking acetylsalicylic acid or enoxaparin.⁵¹ The most common severe pDDI occurred between citalopram and fingolimod ($N=7$ patients, 1.1%). Citalopram accounted for most of the severe interactions ($N=27$) in our study. As a selective serotonin reuptake inhibitor (SSRI), citalopram is often prescribed to patients with anxiety disorders or depression. A side effect of citalopram may cause prolongation of the QT interval, which may lead to ventricular arrhythmias or sudden cardiac death.⁵² Fingolimod is used for the treatment of RRMS, and administration of the first dose may also prolong the QT interval, especially when given concomitantly with SSRIs.⁵³ Thus, citalopram should be avoided within the first days after the start of fingolimod therapy, but afterwards there are no safety concerns so far, so that the actual severity of this pDDI strongly depends on the timing.^{53–55} Although some pDDIs can only be explained theoretically and have not been proven in studies, an assessment of the individual risk factors should still be performed.

Taking into account all degrees of severity, the most common pDDI was a mild interaction between cannabidiol (CBD) and dronabinol (=tetrahydrocannabinol, THC) ($n=41$, 6.5%). CBD and THC are components of *Cannabis sativa*, which is contained in Nabiximols (Sativex®).^{56–58} *Cannabis sativa* is used in MS to improve the symptoms of moderate to severe spasticity and as an off-label treatment for urge incontinence.^{59,60} It was found that both agents can be substrates as well as inhibitors of cytochrome P450 enzymes and thus interact with other medications.⁶¹ Conversely, a change in the activity of the enzymes can lead to higher or lower CBD/THC levels. Due to impaired attention and altered psychomotor abilities, patients taking cannabis should be advised not to engage in safety-related activities requiring full concentration and motor skills, e.g. driving motor vehicles.⁶²

The consideration of pDFIs is important to increase the success of treatments. Pharmacists and clinical staff should therefore pay attention on frequently used drugs that are associated with pDFIs. Foods, beverages and lifestyle factors that can interfere with the effect of medicines include for example alcoholic drinks, grapefruit juice and tobacco smoking. In our study population, we were able to detect 34 severe pDFIs. The most frequent severe pDFI was between ibuprofen and alcohol ($n=105$ patients). It has been shown that regular ibuprofen

users who drink alcoholic beverages have a 2.7-fold higher risk of upper gastrointestinal bleeding compared with nonusers.⁶³ For methylprednisolone, we detected moderate pDFIs with grapefruit (juice) and tobacco. Grapefruit juice can increase the bioavailability of oral methylprednisolone in plasma by 75% but does not significantly affect cortisol plasma concentrations.⁶⁴ Although clinical relevance is low, the effect of methylprednisolone may be enhanced in individuals who ingest a high amount of grapefruit juice.⁶⁴ For dronabinol, a moderate pDFI is described when combined with high-fat food. With regard to bioavailability, an increase in the maximum concentration (in plasma) by a factor of one to three can be observed for dronabinol (administered as a spray) when a high-fat diet is taken.⁶⁵ According to Stott *et al.*⁶⁵ this interaction seems to be clinically less relevant due to interindividual variability. Nevertheless, the doctor should recommend taking dronabinol-containing drugs outside mealtimes in order to avoid possible fluctuations in effect.

Our study cohort well resembled data from the German MS registry (18,030 registered patients) in terms of age (on average, 46.3 years), sex (72% female), median EDSS score (3.0) and disease course distribution.^{66,67} Thelen *et al.*⁶⁸ reported a similar range of patients meeting the criteria for polypharmacy (15–65% of MS patients). An Italian study by Patti *et al.*³⁵ reported a polypharmacy rate of 32.3% in MS patients aged 41–50 years and of 41.2% in patients aged over 50 years. In our previous study of women of child-bearing age with MS, the proportion of patients with polypharmacy was 41.2%.³³

Some limitations of this study should be mentioned. From the structured interviews and the patient records, there is no claim to completeness of the data regarding the number and type of medications used. There is a possibility of a wrongly low/high number of recorded medications as patients often do not exactly know their own medication, or they take additional OTC drugs or CAMs that they do not mention exactly. For instance, patients often fail to mention the use of NSAIDs to their physicians.⁶⁹ Furthermore, adverse reactions because of a pDDI do not necessarily have to occur in a patient, but there is an increased probability. In this study, we did not record adverse drug reactions that actually occurred in the patients. Further limitations are the unknown adherence of drug intake and the

unmeasured individual metabolism characteristics of the patients (e.g. CYP enzyme expression).^{70–72} Our study did not assess the patients' actual dietary pattern, time of food intake or cigarette and alcohol consumption. In further studies, one might explicitly ask MS patients about drug side effects in the following after an initial check of the medication schedules for pDDIs or, if applicable, measure drug levels in the blood to detect pDDIs and pDFIs that actually occur. In the future, deep learning algorithms could improve the prediction of pDDIs and pDFIs.⁷³

Conclusion

In our study of 627 patients with MS, we found at least one pDDI in 408 patients (65.1%). Patients with at least one pDDI were on average 9.4 years older and had 3 years longer disease duration than patients without pDDIs. According to our data, Pw/P are 15 times more likely to have a severe pDDI than Pw/oP. Age and educational level were identified as factors associated with the presence of pDDIs. The most frequent severe pDDI was citalopram \leftrightarrow fingolimod. Therefore, caution is advised when initiating fingolimod therapy in patients using citalopram. Methylprednisolone, acetylsalicylic acid and ibuprofen had the highest pDDI count. This underlines an increased risk of pDDIs from the use of OTC preparations (e.g. acetylsalicylic acid and ibuprofen). In our analysis of pDFIs, 34 severe pDFIs were identified. We found that the combination of ibuprofen and alcohol was the most frequent severe pDFI. Subsequent studies should address dietary habits as well as alcohol and cigarette consumption *via* questionnaires, or, if possible, be substantiated by laboratory tests. This would allow a better assessment of the actual risk of pDFIs to optimise the medication plan of individual patients.

Declarations

Ethics approval and consent to participate

Approval for this study was granted by the ethics committees of the Thuringia Medical Association and the Rostock University Medical Centre (approval numbers A 2014-0089 and A 2019-0048). The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Author contributions

Jane Louisa Debus: Conceptualisation; Data curation; Formal analysis; Methodology; Visualisation; Writing – original draft; Writing – review & editing.

Paula Bachmann: Data curation; Writing – review & editing.

Niklas Frahm: Conceptualisation; Data curation; Methodology; Writing – review & editing.

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Availability of data and material

The data sets generated and analysed in this study are available from the corresponding author on reasonable request.

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Supplemental material

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References

- Voigt N, Ort K and Sossalla S. Drug-drug interactions you should know! *Fortschr Neurol Psychiatr* 2019; 87: 320–332.
- Bjerrum L, Gonzalez Lopez-Valcarcel B and Petersen G. Risk factors for potential drug interactions in general practice. *Eur J Gen Pract* 2008; 14: 23–29.
- Dechanont S, Maphanta S, Butthum B, *et al.* Hospital admissions/visits associated with drug-drug interactions: a systematic review and meta-analysis. *Pharmacoepidemiol Drug Saf* 2014; 23: 489–497.
- Moura CS, Acurcio FA and Belo NO. Drug-drug interactions associated with length of stay and cost of hospitalization. *J Pharm Pharm Sci* 2009; 12: 266–272.
- Sultana J, Cutroneo P and Trifirò G. Clinical and economic burden of adverse drug reactions. *J Pharmacol Pharmacother* 2013; 4(Suppl. 1): S73–S77.
- Ernst FR and Grizzle AJ. Drug-related morbidity and mortality: updating the cost-of-illness model. *J Am Pharm Assoc* 2001; 41: 192–199.
- Magro L, Moretti U and Leone R. Epidemiology and characteristics of adverse drug reactions caused by drug-drug interactions. *Expert Opin Drug Saf* 2012; 11: 83–94.
- Deng J, Zhu X, Chen Z, *et al.* A review of food-drug interactions on oral drug absorption. *Drugs* 2017; 77: 1833–1855.
- Reich DS, Lucchinetti CF and Calabresi PA. Multiple sclerosis. *N Engl J Med* 2018; 378: 169–180.
- GBD 2016 Multiple Sclerosis Collaborators. Global, regional, and national burden of multiple sclerosis 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2019; 18: 269–285.
- Walton C, King R, Rechtman L, *et al.* Rising prevalence of multiple sclerosis worldwide: insights from the Atlas of MS, third edition. *Mult Scler* 2020; 26: 1816–1821.
- Lublin FD, Reingold SC, Cohen JA, *et al.* Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology* 2014; 83: 278–286.
- Zettl UK, Stüve O and Patejdl R. Immune-mediated CNS diseases: a review on nosological classification and clinical features. *Autoimmun Rev* 2012; 11: 167–173.
- Rommer PS, Eichstädt K, Ellenberger D, *et al.* Symptomatology and symptomatic treatment in multiple sclerosis: results from a nationwide MS registry. *Mult Scler* 2019; 25: 1641–1652.
- Hauser SL and Cree BAC. Treatment of multiple sclerosis: a review. *Am J Med* 2020; 133: 1380–1390.e2.
- Toosy A, Ciccarelli O and Thompson A. Symptomatic treatment and management of multiple sclerosis. *Handb Clin Neurol* 2014; 122: 513–562.
- Patejdl R, Penner IK, Noack TK, *et al.* Multiple sclerosis and fatigue: a review on the contribution of inflammation and immune-mediated neurodegeneration. *Autoimmun Rev* 2016; 15: 210–220.
- Patejdl R and Zettl UK. Spasticity in multiple sclerosis: contribution of inflammation, autoimmune mediated neuronal damage and therapeutic interventions. *Autoimmun Rev* 2017; 16: 925–936.
- Rommer PS and Zettl UK. Managing the side effects of multiple sclerosis therapy: pharmacotherapy options for patients. *Expert Opin Pharmacother* 2018; 19: 483–498.
- Rommer P and Zettl UK. Treatment options in multiple sclerosis and neuromyelitis optica spectrum disorders. *Curr Pharm Des* 2022; 28: 428–436.
- Wiendl H, Gold R, Berger T, *et al.* Multiple Sclerosis Therapy Consensus Group (MSTCG): position statement on disease-modifying therapies for multiple sclerosis (white paper). *Ther Adv Neurol Disord* 2021; 14: 17562864211039648.
- Marrie RA. Comorbidity in multiple sclerosis: past, present and future. *Clin Invest Med* 2019; 42: E5–E12.
- Petersen MJ, Bergien SO and Staerk D. A systematic review of possible interactions for herbal medicines and dietary supplements used concomitantly with disease-modifying or symptom-alleviating multiple sclerosis drugs. *Phytother Res* 2021; 35: 3610–3631.

24. Rommer PS, König N, Sühnel A, *et al.* Coping behavior in multiple sclerosis-complementary and alternative medicine: a cross-sectional study. *CNS Neurosci Ther* 2018; 24: 784–789.
25. Kochs L, Wegener S, Sühnel A, *et al.* The use of complementary and alternative medicine in patients with multiple sclerosis: a longitudinal study. *Complement Ther Med* 2014; 22: 166–172.
26. Gotta M, Mayer CA and Huebner J. Use of complementary and alternative medicine in patients with multiple sclerosis in Germany. *Complement Ther Med* 2018; 36: 113–117.
27. Apel A, Greim B, König N, *et al.* Frequency of current utilisation of complementary and alternative medicine by patients with multiple sclerosis. *J Neurol* 2006; 253: 1331–1336.
28. Runia TF, Hop WCJ, Rijke YB, *et al.* Lower serum vitamin D levels are associated with a higher relapse risk in multiple sclerosis. *Neurology* 2012; 79: 261–266.
29. Frahm N, Hecker M and Zettl UK. Multi-drug use among patients with multiple sclerosis: a cross-sectional study of associations to clinicodemographic factors. *Sci Rep* 2019; 9: 3743.
30. Frahm N, Hecker M and Zettl UK. Polypharmacy in chronic neurological diseases: multiple sclerosis, dementia and Parkinson's disease. *Curr Pharm Des* 2021; 27: 4008–4016.
31. Masnoon N, Shakib S, Kalisch-Ellett L, *et al.* What is polypharmacy? A systematic review of definitions. *BMC Geriatr* 2017; 17: 230.
32. Frahm N, Hecker M and Zettl UK. Polypharmacy among patients with multiple sclerosis: a qualitative systematic review. *Expert Opin Drug Saf* 2020; 19: 139–145.
33. Frahm N, Hecker M, Langhorst SE, *et al.* The risk of polypharmacy, comorbidities and drug-drug interactions in women of childbearing age with multiple sclerosis. *Ther Adv Neurol Disord* 2020; 13: 1756286420969501.
34. Thompson AJ, Banwell BL, Barkhof F, *et al.* Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018; 17: 162–173.
35. Patti F, Penaherrera JN, Zieger L, *et al.* Clinical characteristics of middle-aged and older patients with MS treated with interferon beta-1b: post-hoc analysis of a 2-year, prospective, international, observational study. *BMC Neurol* 2021; 21: 324.
36. Bergien SO, Petersen CM, Lynning M, *et al.* Use of natural medicine and dietary supplements concomitant with conventional medicine among people with Multiple Sclerosis. *Mult Scler Relat Disord* 2020; 44: 102197.
37. Doan J, Zakrzewski-Jakubiak H, Roy J, *et al.* Prevalence and risk of potential cytochrome P450-mediated drug-drug interactions in older hospitalized patients with polypharmacy. *Ann Pharmacother* 2013; 47: 324–332.
38. Prely H, Herledan C, Caffin AG, *et al.* Real-life drug-drug and herb-drug interactions in outpatients taking oral anticancer drugs: comparison with databases. *J Cancer Res Clin Oncol* 2022; 148: 707–718.
39. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983; 33: 1444–1452.
40. Bachmann P, Frahm N, Debus JL, *et al.* Prevalence and severity of potential drug–drug interactions in patients with multiple sclerosis with and without polypharmacy. *Pharmaceutics* 2022; 14: 592.
41. Ismail M, Khan S, Khan F, *et al.* Prevalence and significance of potential drug-drug interactions among cancer patients receiving chemotherapy. *BMC Cancer* 2020; 20: 335.
42. Janchawee B, Wongpoowarak W, Owatranporn T, *et al.* Pharmacoepidemiologic study of potential drug interactions in outpatients of a university hospital in Thailand. *J Clin Pharm Ther* 2005; 30: 13–20.
43. Galea I, Ward-Abel N and Heesen C. Relapse in multiple sclerosis. *BMJ* 2015; 350: h1765.
44. Winkelmann A, Loebermann M, Reisinger EC, *et al.* Disease-modifying therapies and infectious risks in multiple sclerosis. *Nat Rev Neurol* 2016; 12: 217–233.
45. Ellenberger D, Eichstädt K, Flachenecker P, *et al.* Decreasing longitudinal use of glucocorticosteroids in multiple sclerosis. *Mult Scler Relat Disord* 2018; 25: 173–174.
46. Rommer PS, Buckow K, Ellenberger D, *et al.* Patients characteristics influencing the longitudinal utilization of steroids in multiple sclerosis – an observational study. *Eur J Clin Invest* 2015; 45: 587–593.
47. Pöllmann W and Feneberg W. Current management of pain associated with multiple sclerosis. *CNS Drugs* 2008; 22: 291–324.
48. Neilley LK, Goodin DS, Goodkin DE, *et al.* Side effect profile of interferon beta-1b in MS: results of an open label trial. *Neurology* 1996; 46: 552–554.
49. Reess J, Haas J, Gabriel K, *et al.* Both paracetamol and ibuprofen are equally effective in managing

- flu-like symptoms in relapsing-remitting multiple sclerosis patients during interferon beta-1a (AVONEX) therapy. *Mult Scler* 2002; 8: 15–18.
50. Walther EU and Hohlfeld R. Multiple sclerosis: side effects of interferon beta therapy and their management. *Neurology* 1999; 53: 1622–1627.
 51. Thérout P, Ouimet H, McCans J, *et al.* Aspirin, heparin, or both to treat acute unstable angina. *N Engl J Med* 1988; 319: 1105–1111.
 52. Maljuric NM, Noordam R, Aarts N, *et al.* Use of selective serotonin re-uptake inhibitors and the heart rate corrected QT interval in a real-life setting: the population-based Rotterdam Study. *Br J Clin Pharmacol* 2015; 80: 698–705.
 53. Bermel RA, Hashmonay R, Meng X, *et al.* Fingolimod first-dose effects in patients with relapsing multiple sclerosis concomitantly receiving selective serotonin-reuptake inhibitors. *Mult Scler Relat Disord* 2015; 4: 273–280.
 54. Camm J, Hla T, Bakshi R, *et al.* Cardiac and vascular effects of fingolimod: mechanistic basis and clinical implications. *Am Heart J* 2014; 168: 632–644.
 55. Bayas A, Schuh K, Baier M, *et al.* Combination treatment of fingolimod with antidepressants in relapsing-remitting multiple sclerosis patients with depression: a multicentre, open-label study – REGAIN. *Ther Adv Neurol Disord* 2016; 9: 378–388.
 56. Novotna A, Mares J, Ratcliffe S, *et al.* A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex®), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. *Eur J Neurol* 2011; 18: 1122–1131.
 57. Flachenecker P, Henze T and Zettl UK. Nabiximols (THC/CBD oromucosal spray, Sativex®) in clinical practice—results of a multicenter, non-interventional study (MOVE 2) in patients with multiple sclerosis spasticity. *Eur Neurol* 2014; 71: 271–279.
 58. Zettl UK, Rommer P, Hipp P, *et al.* Evidence for the efficacy and effectiveness of THC-CBD oromucosal spray in symptom management of patients with spasticity due to multiple sclerosis. *Ther Adv Neurol Disord* 2016; 9: 9–30.
 59. Keating GM. Delta-9-tetrahydrocannabinol/cannabidiol oromucosal spray (Sativex®): a review in multiple sclerosis-related spasticity. *Drugs* 2017; 77: 563–574.
 60. Abo Youssef N, Schneider MP, Mordasini L, *et al.* Cannabinoids for treating neurogenic lower urinary tract dysfunction in patients with multiple sclerosis: a systematic review and meta-analysis. *BJU Int* 2017; 119: 515–521.
 61. Zendluka O, Dovrtělová G, Nosková K, *et al.* Cannabinoids and cytochrome p450 interactions. *Curr Drug Metab* 2016; 17: 206–226.
 62. Brubacher JR, Chan H and Staples JA. Cannabis-impaired driving and Canadian youth. *Paediatr Child Health* 2020; 25(Suppl. 1): S21–S25.
 63. Kaufman DW, Kelly JP, Wiholm BE, *et al.* The risk of acute major upper gastrointestinal bleeding among users of aspirin and ibuprofen at various levels of alcohol consumption. *Am J Gastroenterol* 1999; 94: 3189–3196.
 64. Varis T, Kivistö KT and Neuvonen PJ. Grapefruit juice can increase the plasma concentrations of oral methylprednisolone. *Eur J Clin Pharmacol* 2000; 56: 489–493.
 65. Stott CG, White L, Wright S, *et al.* A phase I study to assess the effect of food on the single dose bioavailability of the THC/CBD oromucosal spray. *Eur J Clin Pharmacol* 2013; 69: 825–834.
 66. Flachenecker P, Eichstädt K, Berger K, *et al.* Multiple Sklerose in Deutschland: aktualisierte Auswertungen des MS-Registers der DMSG 2014–2018. *Fortschr Neurol Psychiatr* 2020; 88: 436–450.
 67. Ohle L-M, Ellenberger D, Flachenecker P, *et al.* Chances and challenges of a long-term data repository in multiple sclerosis: 20th birthday of the German MS registry. *Sci Rep* 2021; 11: 13340.
 68. Thelen J, Zvonarev V, Lam S, *et al.* Polypharmacy in multiple sclerosis: current knowledge and future directions. *Mo Med* 2021; 118: 239–245.
 69. Abdolrasulnia M, Weichold N, Shewchuk R, *et al.* Agreement between medical record documentation and patient-reported use of nonsteroidal antiinflammatory drugs. *Am J Health Syst Pharm* 2006; 63: 744–747.
 70. Zettl UK, Bauer-Steinhusen U, Glaser T, *et al.* Adherence to long-term interferon beta-1b injection therapy in patients with multiple sclerosis using an electronic diary. *Adv Ther* 2016; 33: 834–847.
 71. Zettl UK, Bauer-Steinhusen U, Glaser T, *et al.* Comparative evaluation of patients' and physicians' satisfaction with interferon beta-1b therapy. *BMC Neurol* 2016; 16: 181.
 72. Klauer T and Zettl UK. Compliance, adherence, and the treatment of multiple sclerosis. *J Neurol* 2008; 255(Suppl. 6): 87–92.
 73. Ryu JY, Kim HU and Lee SY. Deep learning improves prediction of drug-drug and drug-food interactions. *Proc Natl Acad Sci USA* 2018; 115: E4304–E4311.

8.3. Publikation 3

Screening for severe drug-drug interactions in patients with multiple sclerosis: A comparison of three drug interaction databases

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Screening for severe drug-drug interactions in patients with multiple sclerosis: A comparison of three drug interaction databases

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Background: Patients with multiple sclerosis (MS) often undergo complex treatment regimens, resulting in an increased risk of polypharmacy and potential drug-drug interactions (pDDIs). Drug interaction databases are useful for identifying pDDIs to support safer medication use.

Objective: To compare three different screening tools regarding the detection and classification of pDDIs in a cohort of MS patients. Furthermore, we aimed at ascertaining sociodemographic and clinical factors that are associated with the occurrence of severe pDDIs.

Methods: The databases Stockley's, Drugs.com and MediQ were used to identify pDDIs by screening the medication schedules of 627 patients. We determined the overlap of the identified pDDIs and the level of agreement in pDDI severity ratings between the three databases. Logistic regression analyses were conducted to determine patient risk factors of having a severe pDDI.

Results: The most different pDDIs were identified using MediQ ($n = 1,161$), followed by Drugs.com ($n = 923$) and Stockley's ($n = 706$). The proportion of pDDIs classified as severe was much higher for Stockley's (37.4%) than for Drugs.com (14.4%) and MediQ (0.9%). Overall, 1,684 different pDDIs were identified by at least one database, of which 318 pDDIs (18.9%) were

Abbreviations: AIC, Akaike information criterion; CAM, complementary and alternative medicines; CDSS, clinical decision support software; CI, confidence interval; CIS, clinically isolated syndrome; CYP, cytochrome P450 superfamily; DDID, drug-drug interaction database; DMD, disease-modifying drug; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; n/N , number; OR, odds ratio; OTC, over-the-counter; pDDI, potential drug-drug interaction; PPMS, primary progressive multiple sclerosis; ref, reference; RRMS, relapsing-remitting multiple sclerosis; Rx, prescription drug; SPMS, secondary progressive multiple sclerosis; SSRI, selective serotonin reuptake inhibitor; VIF, variance inflation factor; vs, versus.

detected with all three databases. Only 55 pDDIs (3.3%) have been reported with the same severity level across all databases. A total of 336 pDDIs were classified as severe (271 pDDIs by one database, 59 by two databases and 6 by three databases). Stockley's and Drugs.com revealed 47 and 23 severe pDDIs, respectively, that were not included in the other databases. At least one severe pDDI was found for 35.2% of the patients. The most common severe pDDI was the combination of acetylsalicylic acid with enoxaparin, and citalopram was the drug most frequently involved in different severe pDDIs. The strongest predictors of having a severe pDDI were a greater number of drugs taken, an older age, living alone, a higher number of comorbidities and a lower educational level.

Conclusions: The information on pDDIs are heterogeneous between the databases examined. More than one resource should be used in clinical practice to evaluate pDDIs. Regular medication reviews and exchange of information between treating physicians can help avoid severe pDDIs.

KEYWORDS

multiple sclerosis, potential drug-drug interactions, drug interaction databases, medication review, therapy management, patient safety

Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease and the most common cause of non-traumatic neurologic disability in young adults (Filippi et al., 2018). A total of 2.8 million people are estimated to live with MS worldwide (Walton et al., 2020). Inflammation with demyelination, astroglial proliferation (reactive gliosis) and neurodegeneration with axonal and synaptic loss are the pathological hallmarks of the disease (Filippi et al., 2018). The course of MS is different in each patient and can be classified into relapsing-remitting MS (RRMS), primary progressive MS (PPMS) and secondary progressive MS (SPMS) (Lublin et al., 2014). The spectrum of MS phenotypes further includes the clinically isolated syndrome (CIS) (Lublin et al., 2014). The clinical manifestations are very heterogeneous (Zettl et al., 2012). Common consequences of MS include impaired mobility, ataxia/tremor, cognitive dysfunction and pain (Larocca, 2011; Rommer et al., 2019a). The symptoms of MS are frustrating for many patients as they severely limit the quality of their daily lives. One therapeutic approach is offered by the use of disease-modifying drugs (DMDs). DMDs can prevent the development of new lesions in the brain and spinal cord, reduce the frequency of relapses and delay the progression of disability (Rommer et al., 2019b; Hauser and Cree, 2020; Rommer and Zettl, 2022). Additionally, patients with MS often take medications to treat specific disease symptoms (Dargahi et al., 2017), medications for comorbidities as well as complementary and alternative medicines (CAMs) such as vitamin and mineral supplements (Apel-Neu and Zettl, 2008; Kochs et al., 2014; Rommer et al., 2018).

As the world population is getting older on average (Aburto et al., 2020), multimorbidity and consequently polypharmacy are

increasingly posing health risks (Payne, 2016; Molokhia and Majeed, 2017). Therefore, interest in potential drug-drug interactions (pDDIs) is rising among physicians, and an appropriate management of medications that may interact is becoming more and more relevant. pDDIs can generally be divided into two different classes: pharmacokinetic and pharmacodynamic interactions. Pharmacokinetic pDDIs affect the liberation, absorption, distribution, metabolism and elimination of drugs, e.g., through the inhibition or induction of metabolic enzymes like the cytochrome P450 (CYP) isozymes or through reduced absorption due to complexation of active substances (Koziolek et al., 2019; Bechtold and Clarke, 2021). Pharmacodynamic pDDIs refer to the influence on the mode of action of drugs, e.g., through additive effect enhancement or antagonistic effect reduction (Niu et al., 2019). In the case of an improper therapy management, there is a risk of overdosed or underdosed therapy, and side effects may occur due to pDDIs.

There are numerous online tools for healthcare professionals and patients to check for pDDIs (Adam and Vang, 2015; Roblek et al., 2015; Kheshti et al., 2016; Hammar et al., 2021). By using these so-called clinical decision support softwares (CDSS) and drug-drug interaction databases (DDIDs), the risk assessment of combined pharmacotherapy is facilitated. This holds greater safety for patients as dangerous pDDIs can be detected and prevented. However, as several pDDI resources have been developed, the question arises which one to use. Physicians and pharmacists should be aware of the differences between pDDI screening tools and know their advantages and limitations. Previous studies have shown relatively low agreement on the classification of pDDIs among different tools, with the overlap being as low as 5% (Amkreutz et al., 2017; Fung et al., 2017; Prely et al., 2022). It is thus often recommended to use more than one

database to increase sensitivity (Smithburger et al., 2010; Wang et al., 2010; Kheshti et al., 2016; Monteith and Glenn, 2019; Sancar et al., 2019; Suriyakorn et al., 2019; Monteith et al., 2020). It should be also noted that DDIDs often label pDDIs with a higher severity rating than bedside clinicians (Armahizer et al., 2013; Roblek et al., 2015).

The occurrence of pDDIs is a highly relevant issue that has been well studied in certain diseases, such as metabolic syndrome (Suriyakorn et al., 2019), bipolar disorder (Monteith et al., 2020) and acquired immunodeficiency syndrome (Ramos et al., 2015). However, with respect to MS, the number of studies on pDDIs is low. We have previously examined pDDIs in female MS patients of childbearing age, with a special focus on interactions that might endanger pregnancy (Frahm et al., 2020a). Moreover, we analyzed the contribution of over-the-counter (OTC) drugs to pDDIs (Bachmann et al., 2022), and we compared the risk of pDDIs between MS patients with and without polypharmacy (Debus et al., 2022). In these studies, either one or two DDIDs were used. To our knowledge, there are so far no other studies on pDDIs in unselected patients with MS.

As there might be disease-specific differences in the performance of pDDI screening tools, we here combined the data from our previous works (Bachmann et al., 2022; Debus et al., 2022) to compare the three databases Stockley's, Drugs.com and MediQ with regard to the identification of pDDIs in MS patients. We further examined the concordance in pDDI severity ratings between the databases. Moreover, we identified the most frequent severe pDDIs in our patients and determined sociodemographic and clinical predictors of having a severe pDDI.

Materials and methods

Study population

The patient survey as part of this study was conducted between March 2017 and May 2020 at the Department of Neurology of the Rostock University Medical Center (Germany) and at the Department of Neurology of the Ecumenic Hainich Hospital Mühlhausen (Germany). The patients had to have a diagnosis of a CIS or MS according to the revised McDonald criteria (Thompson et al., 2018). We included data from adult male and female patients, whereas data from minors under the age of 18 were not included. At both centers, the patients were treated as outpatients or inpatients, depending on the individual disease activity and disease progression. Further information on the design of this cross-sectional study are given elsewhere (Bachmann et al., 2022; Debus et al., 2022).

The patients were interviewed while waiting for outpatient appointments and during inpatient stays due to acute disease exacerbation or changes in therapy. Written informed consent was obtained from all patients who agreed to participate in advance. The ethics committees of the University of Rostock and of the State Medical Association of Thuringia approved this

study (approval numbers A 2014-0089 and A 2019-0048). We conducted this study in accordance with the current Declaration of Helsinki.

Data collection

Sociodemographic data (sex, age, years of schooling, educational level, employment status, partnership status, place of residence, number of children and number of siblings), pharmacological data (medications taken with active ingredient, trade name, route of administration and dosage) and clinical data [comorbidities, course of MS, disease duration and disability level according to Kurtzke's Expanded Disability Status Scale (EDSS)] were obtained using patient records, clinical examinations and structured interviews. The EDSS is the standard instrument for assessing the impairments that can result from MS through neurological examination (Kurtzke, 1983; Kappos et al., 2015). Comorbidity was defined as any additional disease that developed before or during the course of MS and that is not an obvious complication of MS (Magyari and Sorensen, 2020).

From the medication schedules, we captured both on-demand drugs, which are taken irregularly as needed, and long-term drugs, which are taken periodically. More specifically, methylprednisolone was documented as "on-demand drug" when used to treat an acute relapse (Repovic, 2019) and as "long-term drug" when used as repeated pulse therapy for progressive courses of MS (Winkelmann et al., 2016). In addition to recording the use of prescription drugs (Rx), we also explicitly asked the patients about their use of non-prescription drugs (OTC) as well as CAMs like herbal medicines or dietary supplements (Evans et al., 2018; Rommer et al., 2018). Note that some drugs are available as both Rx and OTC preparations, depending on the dosage (e.g., ibuprofen). All drugs were recorded independently of the treatment goals and thus included DMDs for MS, medications to treat disease symptoms as well as medications for comorbidities.

Assessment of potential drug-drug interactions

For the comprehensive analysis of pDDIs, every patient's medication plan was screened using three different DDIDs: Stockley's, Drugs.com and MediQ. Stockley's Interactions Checker is an English-language subscription-based online pDDI tool with over 85,000 deposited interactions. It is published by the Royal Pharmaceutical Society and updated monthly. The pDDI severity levels are divided into three categories: mild (minimal clinical relevance), moderate (moderate clinical relevance) and severe (high clinical relevance) interactions. Furthermore, Stockley's provides information about potential drug-food/beverage/smoking and drug-herb interactions. This tool is based on "Stockley's Drug

Interactions”, the most comprehensive international reference book on drug interactions (Preston, 2020), and primarily aimed at healthcare professionals.

Drugs.com Drug Interactions Checker, edited by the Drugsite Trust, is a free English-language website with information on ~24,000 drugs and herbal medicines. This database classifies pDDIs into three severity levels: minor (minimally clinically significant), moderate (moderately clinically significant) and major (highly clinically significant). The database is aimed at both consumers and medical professionals as explanations of pDDIs are available according to prior medical knowledge. Drugs.com also displays information on potential drug-food/alcohol interactions. A country-restricted mobile app is available. The free accessibility and patient orientation of this DDID clearly sets it apart from other pDDI screening tools.

MediQ is a Swiss web-based tool containing more than 2,000 active substances and more than 50,000 interactions, including not only pDDIs but also drug-food, drug-beverage, and drug-polymorphism interactions (Suter et al., 2013). The latter allow to evaluate the pharmacogenetic effects of patient-specific genetic factors. MediQ is designed for medical staff and is only accessible with a subscription. It is only available in the German language. The pDDI severities are rated as low danger, average danger and high danger of interaction. Furthermore, MediQ distinguishes whether a pDDI is currently ruled out (i.e., there is no known interaction) or whether a drug combination has not yet been assessed by the MediQ operators (i.e., there is no data in the database). Users can request combinations of drugs to be included in the database. MediQ is one of the most commonly used German-language tools for identifying pDDIs. In a study comparing five German-language tools, MediQ was the one with the most complete results (Hahn and Roll, 2018).

The screening for pDDIs was conducted from May 2020 to November 2020 by entering the trade name of each drug in the search field of each database. If the trade name was not found, we entered the generic name(s) of the active ingredient(s) contained in the respective drug. The route of administration (e.g., oral or dermal) was entered as well if possible. pDDIs that were detected in the DDIDs were subsequently recorded in Excel spreadsheets and sorted by severity. To facilitate the interpretation of the database comparisons, we decided to consistently refer to the three pDDI severity levels as mild, moderate and severe as they are called in Stockley’s, instead of using different labels (such as minor/low) per database. With regard to MediQ, we considered the category “no data available” as equivalent to the category “no known interaction” for simplicity.

Data analysis

The data were prepared with IBM SPSS Statistics version 27, Microsoft Excel 2010 and ONLYOFFICE 7.0. Descriptive statistics and further data analyses were performed in R version 3.6.0. We first determined the number of different

pDDIs (i.e., without repetitions if they occurred in more than one patient) found with Stockley’s, Drugs.com and MediQ. The relative proportions of mild, moderate and severe pDDIs per database were then visualized using doughnut plots. The overlap of pDDIs from the 3 databases was analyzed with the R package VennDiagram (Chen and Boutros, 2011). Concordance rates were calculated by dividing the number of identical pDDI severity ratings by the number of pDDIs that were detected in each of two databases being compared. Cohen’s kappa coefficients (κ) were also computed to summarize the agreement among the databases. The severe pDDIs were drawn as a network using Cytoscape 3.9.0 (Shannon et al., 2003) with yFiles layout algorithms. Binary logistic regression analyses were performed to predict the patients’ risk of having a severe pDDI. The numerical, ordinal and dichotomous variables were included either separately (univariable models) or jointly (multivariable model). The latter was performed by bidirectional stepwise model selection based on the Akaike information criterion (AIC) (Akaike and Lovric, 2011) using the R package MASS. The resulting odds ratios (ORs) were visualized as forest plots with the R packages sjPlot and ggplot2 (Wickham, 2016). The corresponding statistical tests were exploratory in nature, and therefore the significance level was set at $\alpha = 0.05$. We checked for collinearities in the data by calculating the variance inflation factor (VIF) for each independent variable with the mctest R package. Scatterplots were used to display the relationship between age and number of drugs taken with pDDI count. Exponential curves were fitted to the data, and 95% confidence intervals of the fitted curves were calculated by performing bootstrap resampling.

Results

Patient cohort

A total of 627 patients were included in this study (Table 1). The patient cohort was composed of cases with CIS ($n = 27$), RRMS ($n = 388$), SPMS ($n = 154$), and PPMS ($n = 58$). The proportion of women was 70.3% ($n = 441$). The age of the patients ranged from 19 to 86 years (mean \pm standard deviation: 48.6 ± 13.3). There were 465 patients (74.2%) who lived in a partnership and 162 patients (25.8%) who lived alone. A large proportion of the subjects resided in a rural area ($n = 224$), whereas the others lived in a provincial town ($n = 108$), medium-sized town ($n = 112$) or city ($n = 183$). With regard to the level of education, the patients had either no training ($n = 19$), a qualification as a skilled worker ($n = 398$) or a degree from a technical college ($n = 89$) or university ($n = 121$). The average EDSS score of the patients was 3.6 ± 2.1 (range: 0–9) at a median disease duration of 10 years (range: 0–52). Most of the patients ($n = 443$, 70.7%) had comorbidities in addition to MS. Only seven and 52 patients received no or only one drug, respectively, whereas most patients ($n = 568$, 90.6%) took at least two drugs and

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TABLE 1 Sociodemographic, clinical and medication data of the patient cohort (N = 627).

Parameter	N (%) or range	Mean (SD) or median
Sex		
Female	441 (70.3%)	
Male	186 (29.7%)	
Age [in years]	19–86	48.6 (13.3)
School years	6–18	10.5 (1.3)
Educational level		
No training	19 (3.0%)	
Skilled worker	398 (63.5%)	
Technical college	89 (14.2%)	
University	121 (19.3%)	
Employment status		
In training	7 (1.1%)	
In studies	6 (1.0%)	
Employed	269 (42.9%)	
Unemployed	25 (4.0%)	
Retired	304 (48.5%)	
Others	16 (2.6%)	
Partnership		
No	162 (25.8%)	
Yes	465 (74.2%)	
Place of residence		
Rural area	224 (35.7%)	
Provincial town	108 (17.2%)	
Medium-sized town	112 (17.9%)	
City	183 (29.2%)	
Number of children	0–4	1
0	169 (27.0%)	
1	170 (27.1%)	
≥2	288 (45.9%)	
Number of siblings	0–13	1
0	71 (11.3%)	
1	305 (48.6%)	
≥ 2	251 (40.0%)	
EDSS score [points]	0–9.0	3.5
Disease duration [in years]	0–52	10
Disease course		
CIS	27 (4.3%)	
RRMS	388 (61.9%)	
SPMS	154 (24.6%)	
PPMS	58 (9.3%)	
Comorbidities	0–9	1
No	184 (29.3%)	
Yes	443 (70.7%)	
Number of drugs taken	0–19	5
0	7 (1.1%)	
1–4	286 (45.6%)	
5–9	261 (41.6%)	
≥ 10	73 (11.6%)	

CIS, clinically isolated syndrome; EDSS, Expanded Disability Status Scale; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation; SPMS, secondary progressive multiple sclerosis.

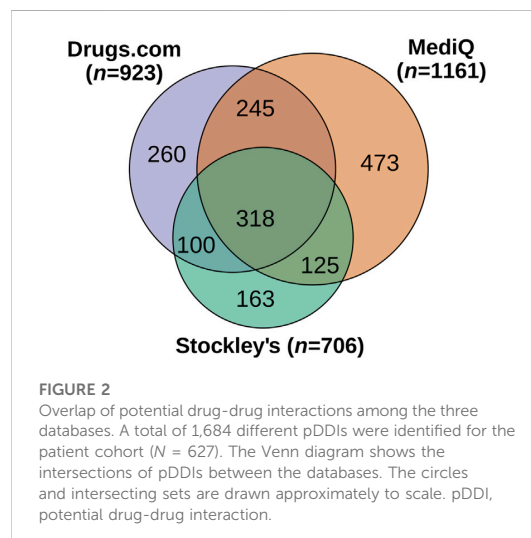
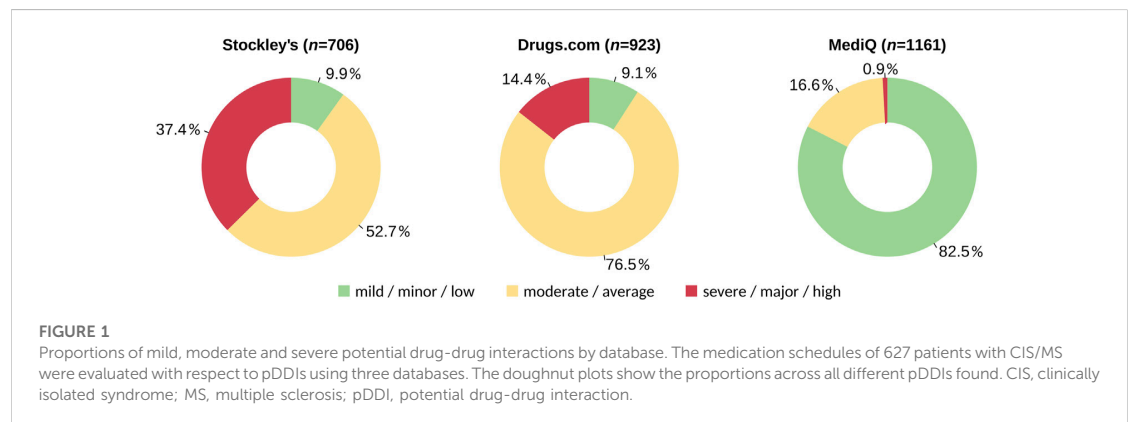
thus were at risk of pDDIs. The average number of drugs taken per patient was 5.3 ± 3.3 (range: 0–19). For further details on the clinical, demographic and medication data of the patients, the reader is referred to our previous publications (Bachmann et al., 2022; Debus et al., 2022).

Comparison of potential drug-drug interactions information from different sources

The database-driven screening revealed pDDIs for 280 different drugs. We found 706 different pDDIs with Stockley's, 923 different pDDIs with Drugs.com and 1,161 different pDDIs with MediQ. However, while fewer pDDIs were found using Stockley's, 264 of the pDDIs from this database (37.4%) were rated as severe. In comparison, only 10 of the pDDIs from MediQ (0.9%) were classified as severe (Figure 1). In total, 1,684 different pDDIs were identified with the three drug interaction databases. The consistency in detecting pDDIs was relatively low: Only 318 pDDIs (18.9%) were reported in all databases, and each database specified pDDIs that were not contained in the other two databases. The largest overlap was noticed for Drugs.com vs. MediQ (563 different pDDIs) (Figure 2). With regard to the pDDI severity ratings, there was a greater agreement for Drugs.com vs. Stockley's. For these, the severity ratings concordance rate was 60.0%. The respective rate was lower for Drugs.com vs. MediQ (23.3%) and MediQ vs. Stockley's (24.2%) because the pDDIs were typically reported with a lower severity in MediQ (Figure 3). As many as 110 different pDDIs that were classified as mild in MediQ were severe according to Stockley's. On the other hand, there were three severe pDDIs from MediQ that were not detected with Stockley's (amantadine < = > amitriptyline, cannabidiol < = > sertraline and citalopram < = > tamoxifen). Only 55 of the 1,684 different pDDIs (3.3%) have been reported with the same severity level across all databases (i.e., 17.3% of the 318 common pDDIs).

Severe potential drug-drug interactions in patients with multiple sclerosis

The number of different severe pDDIs was 264 for Stockley's, 133 for Drugs.com and 10 for MediQ. Overall, 336 different pDDIs were severe according to at least one of the databases (Supplementary Figure S1). A subset of 271 pDDIs were classified as severe in only one database, 59 pDDIs were classified as severe in two databases and six pDDIs were consistently classified as severe in all three databases (citalopram with ciprofloxacin, doxepin, flecainide, levofloxacin, ondansetron and quetiapine). Citalopram was involved in 33 different severe pDDIs. Ibuprofen and methylprednisolone were also frequently involved in pDDIs, with 23 and 22 severe pDDIs, respectively. Forty-three severe



pDDIs occurred in three or more of the 627 patients (Table 2). The most common severe pDDI was acetylsalicylic acid < = > enoxaparin, which was recorded for 21 patients. Stockley's and Drugs.com yielded 47 and 23 severe pDDIs, respectively, that were not included in the other databases (Table 3). Among the drugs that were associated with severe pDDIs, there were also several DMDs for the therapy of MS: cladribine, fingolimod, interferon beta, mitoxantrone, natalizumab and teriflunomide.

Factors associated with the risk of having a severe potential drug-drug interactions

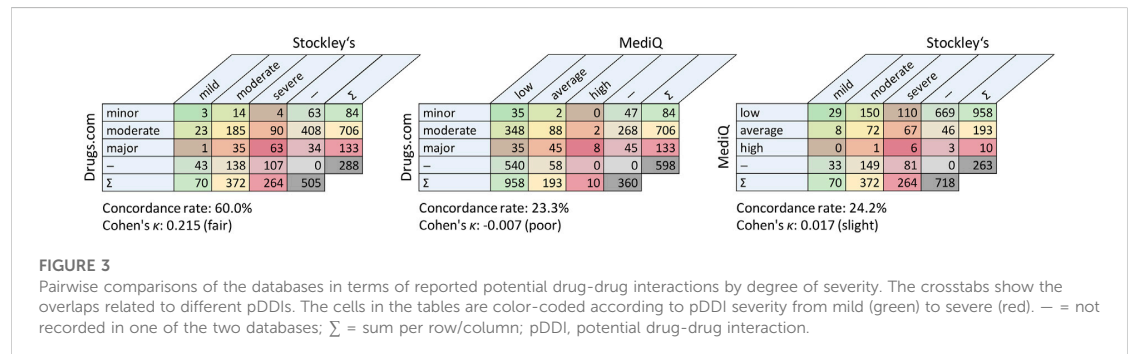
Over all patients, we identified an average of 5.7 ± 9.4 pDDIs (0.9 ± 2.0 severe pDDIs) that were reported in at least one of the

three drug interaction databases. For 441 of the 627 patients (70.3%), we found at least one pDDI, and for 221 patients (35.2%), we found at least one severe pDDI. The latter number is essentially the result of using Drugs.com and Stockley's as only a small subset of 11 patients were found to have a severe pDDI according to MediQ.

The logistic regression analyses revealed predictors of the risk of having at least one severe pDDI. In the univariable models, statistically significant ORs >1 were obtained for age and disease duration, number of children and siblings, degree of disability (EDSS score), comorbidities as well as the number of drugs taken. Conversely, more years in school, a higher educational level and living in a partnership turned out to be protective factors with significant ORs < 1 (Figure 4). In the multivariable model, age, educational level, partnership status, comorbidities and number of drugs taken remained as significantly associated with the risk of having a severe pDDI. Multicollinearity was not detected in the data (VIF < 1.81). The particularly strong relationships between age and number of drugs taken with pDDI count are shown in Figure 5. Remarkably, one female SPMS patient taking 19 drugs had as many as 70 pDDIs, 22 of which were severe pDDIs. Another woman with SPMS received only four drugs (citalopram, mitoxantrone, ondansetron and solifenacin) but nonetheless had six severe pDDIs (all possible pairwise drug combinations) according to Stockley's.

Discussion

Patients with MS are typically treated with a broad spectrum of medications. In addition to DMDs, symptomatic drugs and CAMs are often used to alleviate the symptoms of MS, while comorbidities need to be treated with medications as well. This poses a significant risk of pDDIs, which can lead to adverse health outcomes. Therefore, as part of the therapy management, it should be regularly checked whether pDDIs are present, e.g.,



using pDDI screening tools. To provide insights into their utility, we here compared the databases Stockley's, Drugs.com and MediQ with respect to differences in the detection and rating of pDDIs in patients with MS. We found that the databases provide quite heterogeneous information and that each database reports pDDIs that are not recorded in the other two databases. Beyond this database comparison, we discuss below the most frequent severe pDDIs identified in our patients and highlight sociodemographic and clinical characteristics that were associated with the occurrence of severe pDDIs.

With an average age of 48.6 years, a sex ratio of approximately 2.4 (female) to 1 (male) and a proportion of patients with relapsing-onset MS of ~90%, our study cohort compares well with large national MS cohorts (Boström et al., 2013; Weih et al., 2020; Ohle et al., 2021). We thus believe that we can to some extent generalize the results of our study to a wider population of patients with MS. After combining the information from the three databases, the analysis revealed a prevalence of 70.3% and 35.2% of having ≥ 1 pDDI and ≥ 1 severe pDDI, respectively. However, only 18.9% of all different pDDIs were detected with all three pDDI screening tools used. It has been previously shown that there are large variations between CDSS/DDIDs concerning severity ratings and the documentation of information related to clinical effects, mechanism and management of pDDIs (Wang et al., 2010; Monteith and Glenn, 2019; Shariff et al., 2021). In fact, in studies comparing different pDDI programs and databases, the overlap of pDDIs that were detected in all resources ranged between 5% and 44% (Vonbach et al., 2008; Smithburger et al., 2010; Smithburger et al., 2012; Amkreutz et al., 2017; Fung et al., 2017; Sancar et al., 2019; Suriyapakorn et al., 2019; Tecen-Yucel et al., 2020; Prely et al., 2022). We found the lowest concordance rate for Drugs.com vs. MediQ (23.3%), and only 3.3% of the different pDDIs were recorded and classified with the same severity in all three databases. This finding is similar to earlier studies by Smithburger et al. (2010) who reported that the interaction databases Micromedex and Lexi-Interact agreed on the severity ratings in only ~20% of the pDDIs and that some

major pDDIs occurring in intensive care units were identified in only one of the two databases (Smithburger et al., 2012). In another study comparing Micromedex, Medscape and Drugs.com in the community pharmacy setting, 13.1% of all different pDDIs were scored with the same severity level in all three programs (Sancar et al., 2019).

There are multiple reasons for the limited overlap and concordance between the three databases considered in our study. First of all, there is no standardized definition of a pDDI (Hines et al., 2012), which leads to different views on what might be a pDDI and what not. Different databases may be based on different sources of information and set different requirements for the level of evidence to define a pDDI for a drug combination. Case reports may be sufficient for one database, while other databases may rather rely on pharmacokinetic properties (e.g., knowledge of CYP isozymes involved in the metabolism of the drugs) or studies on pharmacodynamic responses. Whether a drug interacts with another often depends on various factors (e.g., drug intake interval, dose and route of administration), which are not uniformly taken into account in the databases. With regard to the severity rating of pDDIs, there is also no consistent definition of, e.g., a mild pDDI. Another possible explanation for the diverging results is the different target group of each resource. MediQ is targeted at medical professionals and is intended for everyday clinical use, whereas Drugs.com is mainly build for patients and non-medical people. Drugs.com might therefore be more restrained in showing pDDIs than MediQ, because medical laypersons are usually less interested in any mild pDDI that might occur under certain circumstances and they would be otherwise confused by the amount of information (Weingart et al., 2003; Kusch et al., 2018). For patients, it is more important that they will be informed on possibly severe pDDIs so that they visit their doctor once more rather than not often enough, even if the likelihood of a pDDI to be actually life-threatening is low (Hammar et al., 2021). It also has to be considered that the databases are not equally complete regarding drugs and pDDIs recorded. For instance, in Drugs.com, dimetindene or fenoterol

TABLE 2 Severe potential drug-drug interactions that were found for at least 3 patients.

Drug-drug interaction	Stockley's	Drugs.com	MediQ	Frequency, n (%)
Acetylsalicylic acid < = > Enoxaparin	moderate	severe	moderate	21 (3.3%)
Enoxaparin < = > Ibuprofen	moderate	severe	moderate	16 (2.6%)
Baclofen < = > Ibuprofen	severe	—	mild	15 (2.4%)
Ibuprofen < = > Methylprednisolone	severe	moderate	—	14 (2.2%)
Enoxaparin < = > Ramipril	severe	moderate	mild	13 (2.1%)
Citalopram < = > Methylprednisolone	severe	—	moderate	10 (1.6%)
Dipyron/metamizole < = > Methylprednisolone	severe	—	mild	9 (1.4%)
Methylprednisolone < = > Solifenacin	severe	—	—	9 (1.4%)
Acetaminophen/paracetamol < = > Ibuprofen	severe	—	mild	7 (1.1%)
Citalopram < = > Fingolimod	severe	severe	moderate	7 (1.1%)
Interferon beta-1a < = > Ramipril	severe	moderate	—	7 (1.1%)
Mitoxantrone < = > Ondansetron	severe	—	—	7 (1.1%)
Acetylsalicylic acid < = > Ibuprofen	severe	severe	moderate	6 (1.0%)
Amlodipine < = > Simvastatin	mild	severe	moderate	6 (1.0%)
Citalopram < = > Ibuprofen	severe	moderate	mild	6 (1.0%)
Ibuprofen < = > Teriflunomide	—	severe	—	6 (1.0%)
Acetylsalicylic acid < = > Dipyron/metamizole	severe	—	moderate	5 (0.8%)
Citalopram < = > Solifenacin	severe	severe	moderate	5 (0.8%)
Methylprednisolone < = > Tizanidine	severe	—	—	5 (0.8%)
Acetylsalicylic acid < = > Duloxetine	severe	moderate	mild	4 (0.6%)
Candesartan < = > Enoxaparin	severe	moderate	mild	4 (0.6%)
Citalopram < = > Fampridine	severe	—	—	4 (0.6%)
Diclofenac < = > Enoxaparin	moderate	severe	moderate	4 (0.6%)
Diclofenac < = > Methylprednisolone	severe	moderate	—	4 (0.6%)
Escitalopram < = > Pantoprazole	severe	—	mild	4 (0.6%)
Ramipril < = > Teriflunomide	—	severe	—	4 (0.6%)
Ramipril < = > Tizanidine	moderate	severe	mild	4 (0.6%)
Acetylsalicylic acid < = > Teriflunomide	—	severe	mild	3 (0.5%)
Acetylsalicylic acid < = > Venlafaxine	severe	moderate	mild	3 (0.5%)
Amlodipine < = > Magnesium	severe	—	—	3 (0.5%)
Baclofen < = > Levodopa	severe	moderate	moderate	3 (0.5%)
Bisoprolol < = > Tamsulosin	severe	—	mild	3 (0.5%)
Ciprofloxacin < = > Methylprednisolone	severe	severe	mild	3 (0.5%)
Citalopram < = > Dronabinol	severe	moderate	mild	3 (0.5%)
Citalopram < = > Mitoxantrone	severe	—	—	3 (0.5%)
Duloxetine < = > Ibuprofen	severe	moderate	mild	3 (0.5%)
Enoxaparin < = > Valsartan	severe	moderate	mild	3 (0.5%)
Escitalopram < = > Fingolimod	severe	severe	moderate	3 (0.5%)
Escitalopram < = > Ibuprofen	severe	moderate	mild	3 (0.5%)
Insulin glargine < = > Ramipril	severe	moderate	mild	3 (0.5%)
Methylprednisolone < = > Teriflunomide	—	severe	—	3 (0.5%)
Mitoxantrone < = > Solifenacin	severe	—	—	3 (0.5%)
Solifenacin < = > Torasemide	severe	—	—	3 (0.5%)

The medication schedules of a total of 627 patients with CIS/MS were evaluated using three drug interaction databases. This table lists 43 pDDIs (sorted by frequency) that were classified as severe in at least one of the databases and that were found for $n \geq 3$ patients. Please note that the severity levels from Drugs.com (minor, moderate and major) and MediQ (low, average and high) were relabeled here according to those from Stockley's. Disease-modifying drugs for MS are marked in bold. — = not recorded in the database; CIS, clinically isolated syndrome; MS, multiple sclerosis; pDDI, potential drug-drug interaction.

TABLE 3 Potential drug-drug interactions detected in only one database and classified as severe.

Severe pDDIs according to Stockley's only	Frequency, <i>n</i> (%)	Severe pDDIs according to Drugs.com only	Frequency, <i>n</i> (%)
Methylprednisolone < = > Solifenacin	9 (1.4%)	Ibuprofen < = > Teriflunomide	6 (1.0%)
Mitoxantrone < = > Ondansetron	7 (1.1%)	Ramipril < = > Teriflunomide	4 (0.6%)
Methylprednisolone < = > Tizanidine	5 (0.8%)	Methylprednisolone < = > Teriflunomide	3 (0.5%)
Citalopram < = > Fampridine	4 (0.6%)	Candesartan < = > Potassium	2 (0.3%)
Amlodipine < = > Magnesium	3 (0.5%)	Cannabidiol < = > Teriflunomide	2 (0.3%)
Citalopram < = > Mitoxantrone	3 (0.5%)	Fingolimod < = > Methylprednisolone	2 (0.3%)
Mitoxantrone < = > Solifenacin	3 (0.5%)	Acetaminophen/paracetamol < = > Leflunomide	1 (0.2%)
Solifenacin < = > Torasemide	3 (0.5%)	Acetaminophen/paracetamol < = > Teriflunomide	1 (0.2%)
Dipyron/metamizole < = > Prednisolone	2 (0.3%)	Acetylsalicylic acid < = > Brinzolamide	1 (0.2%)
Escitalopram < = > Fampridine	2 (0.3%)	Acetylsalicylic acid < = > Dorzolamide	1 (0.2%)
Mitoxantrone < = > Tolterodine	2 (0.3%)	Budesonide < = > Natalizumab	1 (0.2%)
Mitoxantrone < = > Torasemide	2 (0.3%)	Captopril < = > Teriflunomide	1 (0.2%)
Sodium < = > Torasemide	2 (0.3%)	Cladribine < = > Fluticasone	1 (0.2%)
Timolol < = > Travoprost	2 (0.3%)	Codeine < = > Tizanidine	1 (0.2%)
Beclomethasone < = > Escitalopram	1 (0.2%)	Diclofenac < = > Teriflunomide	1 (0.2%)
Betamethasone < = > Dipyron/metamizole	1 (0.2%)	Dimenhydrinate < = > Potassium citrate	1 (0.2%)
Betamethasone < = > Fenoterol	1 (0.2%)	Fingolimod < = > Tamoxifen	1 (0.2%)
Betamethasone < = > Fluconazole	1 (0.2%)	Ibuprofen < = > Immunoglobulin G	1 (0.2%)
Betamethasone < = > Formoterol	1 (0.2%)	Irbesartan < = > Potassium	1 (0.2%)
Bicalutamid < = > Goserelin	1 (0.2%)	Mirabegron < = > Tamoxifen	1 (0.2%)
Bicalutamid < = > Triptorelin	1 (0.2%)	Potassium < = > Solifenacin	1 (0.2%)
Budesonide < = > Venlafaxine	1 (0.2%)	Quetiapine < = > Tapentadol	1 (0.2%)
Caffeine < = > Paroxetine	1 (0.2%)	Topiramate < = > Trospium chloride	1 (0.2%)
Candesartan < = > Ramipril	1 (0.2%)		
Citalopram < = > Fludrocortisone	1 (0.2%)		
Citalopram < = > Hydrocortisone	1 (0.2%)		
Citalopram < = > Xipamide	1 (0.2%)		
Dexamethasone < = > Opipramol	1 (0.2%)		
Dydrogesterone < = > Topiramate	1 (0.2%)		
Eprosartan < = > Tamsulosin	1 (0.2%)		
Escitalopram < = > Methylprednisolone	1 (0.2%)		
Etofenamate < = > Fluoxetine	1 (0.2%)		
Etoricoxib < = > Methylprednisolone	1 (0.2%)		
Fenoterol < = > Fluconazole	1 (0.2%)		
Fingolimod < = > Sulpiride	1 (0.2%)		
Fingolimod < = > Tolterodine	1 (0.2%)		
Fludrocortisone < = > Solifenacin	1 (0.2%)		
Furosemide < = > Levofloxacin	1 (0.2%)		
Hydrocortisone < = > Solifenacin	1 (0.2%)		
Hydrocortisone < = > Tolterodine	1 (0.2%)		
Latanoprost < = > Timolol	1 (0.2%)		
Lovastatin < = > Niacin	1 (0.2%)		
Methylprednisolone < = > Quinine sulfate	1 (0.2%)		
Mitoxantrone < = > Tizanidine	1 (0.2%)		
Prednisolone < = > Solifenacin	1 (0.2%)		
Simvastatin < = > Sitagliptin	1 (0.2%)		
Tolterodine < = > Torasemide	1 (0.2%)		

In the dataset of 627 patients, we found 47 severe pDDIs in the Stockley's database that were not listed in the other two databases. Similarly, we found 23 severe pDDIs in the Drugs.com database that were not listed in the other two databases. Among the 473 pDDIs that were found exclusively in the MediQ database, there was no severe pDDI. Disease-modifying drugs for multiple sclerosis are marked in bold. pDDI, potential drug-drug interaction.

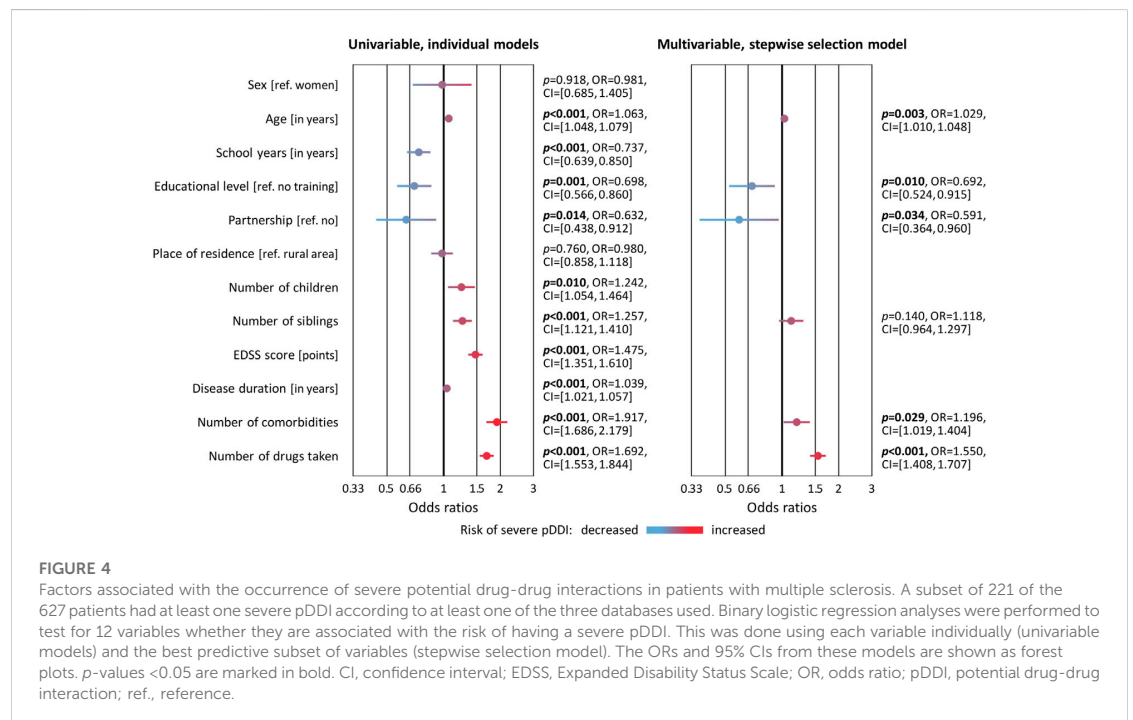


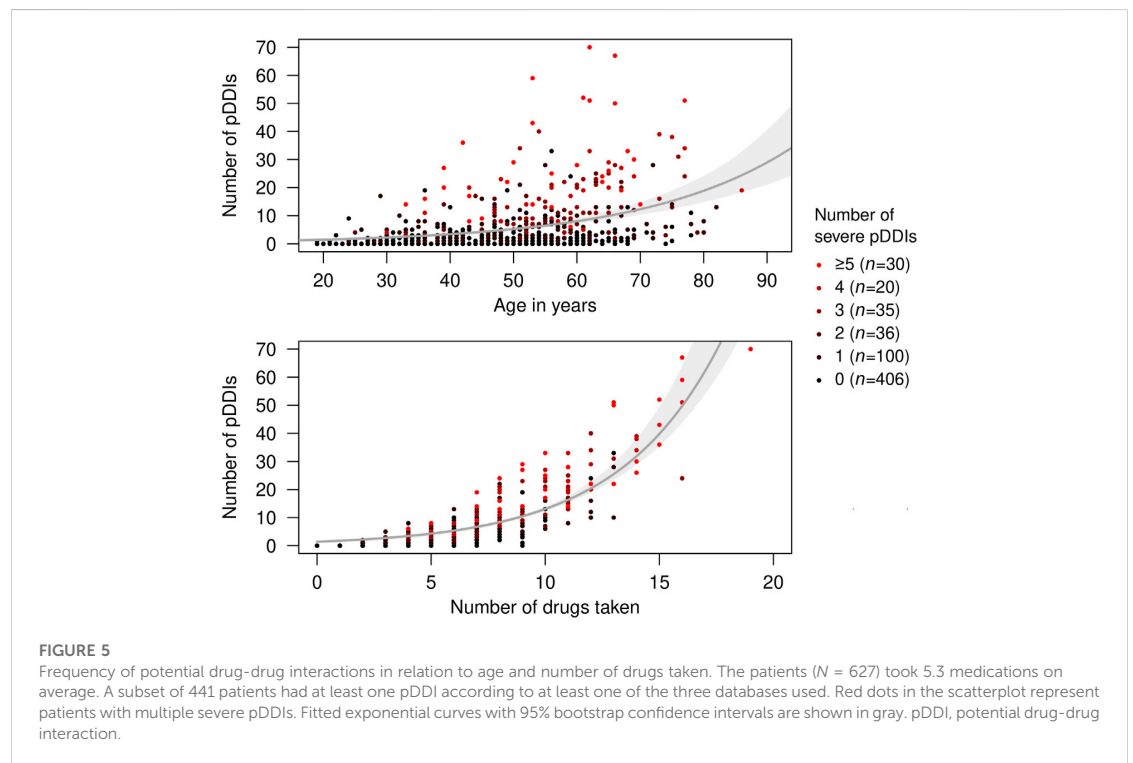
FIGURE 4

Factors associated with the occurrence of severe potential drug-drug interactions in patients with multiple sclerosis. A subset of 221 of the 627 patients had at least one severe pDDI according to at least one of the three databases used. Binary logistic regression analyses were performed to test for 12 variables whether they are associated with the risk of having a severe pDDI. This was done using each variable individually (univariable models) and the best predictive subset of variables (stepwise selection model). The ORs and 95% CIs from these models are shown as forest plots. p -values < 0.05 are marked in bold. CI, confidence interval; EDSS, Expanded Disability Status Scale; OR, odds ratio; pDDI, potential drug-drug interaction; ref., reference.

were not found and pDDIs could therefore not be determined for those. The update intervals differ and, therefore, a given pDDI might be documented differently across the databases. There is also typically more information on drugs that have been approved for a longer time (such as interferon beta) than for newer drugs (such as cladribine). For clinicians, it is thus currently recommended to use more than one CDSS/DDID and to consult a clinical pharmacist in order not to miss relevant pDDIs (Smithburger et al., 2010; Wang et al., 2010; Kheshti et al., 2016; Sancar et al., 2019; Suriyakorn et al., 2019).

Severe pDDIs can lead to life-threatening conditions and require medical intervention to prevent serious consequences (Sheikh-Taha and Asmar, 2021). In our study, a total of 336 pDDIs were classified as severe in at least one database. The most common severe pDDI was acetylsalicylic acid with enoxaparin. This combination may lead to an increased bleeding tendency (Theroux et al., 1988). Citalopram, a selective serotonin reuptake inhibitor (SSRI), was most frequently involved in severe pDDIs. This finding is similar to a study on severe pDDIs in patients with dementia, according to which citalopram was involved in half of the top ten severe pDDIs (Bogetti-Salazar et al., 2016). We found severe pDDIs with citalopram for 33 different drugs, including mitoxantrone, fingolimod, acetylsalicylic acid, isoniazid and solifenacin. Citalopram is metabolized by the CYP2C19 enzyme, which is increased in activity after acetylsalicylic acid intake (Chen et al., 2003) but

inhibited by isoniazid (Desta et al., 2001). Therefore, it may be appropriate to monitor the levels of citalopram in plasma or serum in the early phase of treatment. Dose adjustments may prevent later treatment failure and adverse drug reactions (Ostad Haji et al., 2013). The therapeutic reference range for citalopram is between 50 and 110 ng/ml, while concentrations > 220 ng/ml are considered to be above the “laboratory alert level” (Hiemke et al., 2018). Apart from pharmacokinetic interactions, SSRI medications are associated with a modest increase in the risk of gastrointestinal bleeding, and when used in combination with non-steroidal anti-inflammatory drugs (e.g., acetylsalicylic acid) or oral anticoagulants (e.g., phenprocoumon) the risk of bleeding complications is elevated (Anglin et al., 2014; Nochaiwong et al., 2022). Therefore, co-prescription should be weighed by a risk-benefit assessment. Solifenacin is used to relieve symptoms of an overactive bladder in patients with MS (van Rey and Heesakkers, 2011), but it may in rare cases cause a prolongation of the QT interval (Bray and Hancox, 2017). Citalopram also causes a dose-dependent QT interval prolongation (Maljuric et al., 2015). Hence, concurrent administration of citalopram and solifenacin can result in a higher risk of cardiac arrhythmias (Behr and Roden, 2013). Due to the relatively high prevalence of depressive and anxiety disorders in patients with MS (up to 50%), antidepressants such as SSRIs are often prescribed (Patten et al., 2017). To prevent severe pDDIs, individualized therapy with antidepressants should thus be implemented with critical



indication and consideration of alternatives (Stamoula et al., 2021).

We found several severe pDDIs involving DMDs, e.g., teriflunomide, fingolimod, mitoxantrone and interferon beta. For the corticosteroid methylprednisolone, we found severe pDDIs with fingolimod and teriflunomide in Drugs.com. Fingolimod reversibly reduces the number of circulating lymphocytes, while teriflunomide reduces the proliferation of activated B and T lymphocytes (Bar-Or and Li, 2021). Studies found no generally increased risk of infections in patients treated with fingolimod or teriflunomide (Francis et al., 2014; Winkelmann et al., 2016; Winkelmann et al., 2022). However, concurrent use of immunomodulatory or immunosuppressive therapies can have additive effects on the immune system, thereby increasing infectious risks. Therefore, corticosteroid treatment for relapses should be limited (3–5 days) in MS patients receiving DMDs, and a decision for prolonged or repeated high-dose corticosteroid use should be made on an individual basis after careful consideration (Arvin et al., 2015; Abrantes et al., 2021). The pDDI resulting from the combination of citalopram with fingolimod was classified as severe due to the risk of ventricular arrhythmias, but clinical studies revealed no additional risk of abnormal electrocardiogram findings in patients who received fingolimod and SSRIs compared with

patients receiving fingolimod therapy alone (Bermel et al., 2015; Bayas et al., 2016).

Older age and a higher number of comorbidities were strong risk factors for the occurrence of severe pDDIs according to the multivariable model. Furthermore, we found severe pDDIs more frequently in MS patients with a lower educational level and in patients who were not in a partnership. This is in line with previous studies by our group and others showing that with older age and the presence of comorbidities, the number of drugs taken increases on average (Frahm et al., 2019; Frahm et al., 2020b; Zanghi et al., 2021; Bachmann et al., 2022) and so does the risk of pDDIs (Debus et al., 2022). Our analysis also complements the results of studies not related to MS. An Irish study of elderly community dwellers found that patients with a higher educational level were less likely to have severe pDDIs (Hughes et al., 2021). In patients with dementia, factors that were associated with severe pDDIs were taking a greater number of drugs, depression, dementia severity and caregiver burden (Bogetti-Salazar et al., 2016).

To prevent adverse drug reactions due to (severe) pDDIs, the treating physicians should regularly review the current medication plan and educate the patient well about the correct use of drugs (e.g., dosage and intake interval) and side effects that may occur (Tannenbaum and Sheehan, 2014). In this

effort, the physicians should not only pay attention to the medications they prescribed, but should also place these in a critical context with the medications prescribed by physicians from other specialties. When checking for pDDIs, the use of OTC drugs should not be neglected (Scherf-Clavel, 2022) as, according to our previous study, about one in five pDDIs is related to OTC medicines in patients with MS (Bachmann et al., 2022). If a clinically relevant pDDI is identified, there are various options for dealing with it. Rx and OTC medications that are not necessary for the patient can be discontinued. Depending on the need, the use of a drug can also be reduced or just temporarily suspended. Substitution of a drug with an alternative, less interacting drug might also be conceivable. If all this is not possible after weighing the risks, a close therapy monitoring supported by laboratory tests and a detailed counseling of the patient should be ensured. It is particularly important that the patient knows the typical first signs of adverse events associated with an unavoidable pDDI so that a physician consultation is sought quickly if the need arises. A close cooperation between different medical disciplines and between physicians and pharmacists should be understood as the basis for improving individualized patient care.

Our study has several limitations. First, the data were collected at medical centers in Germany, but internationally, there are differences in the therapeutic management of patients with MS and in the provision and reimbursement of drugs. When collecting the medication data, it was ensured that the data were recorded twice (*via* the patient interview and the patient record). Nevertheless, there is always a risk of inaccuracies when analyzing medication schedules. For the evaluation of pDDIs, we here gathered and compared information from three selected commonly used databases. The discussed severe pDDIs therefore do not necessarily represent an exhaustive list of all severe pDDIs that may occur in MS patients. In the present study, we did not investigate possible drug-food and drug-gene interactions. Moreover, we did not examine whether the treating physicians were already aware of the pDDIs and whether they considered them as not clinically relevant. Some of the identified pDDIs are based on theoretical mechanisms involving known CYP enzyme substrates, inducers or inhibitors, but are currently without solid evidence to affirm the theoretical interaction (by clinically relevant case reports). We cannot state to what extent the differences in the detection of pDDIs between the databases were due to insufficient data on the pharmacokinetics or pharmacodynamics of the drugs. The mechanisms of action of individual pDDIs were reported quite differently in the databases. In some cases only pharmacokinetic mechanisms were explained, in others only pharmacodynamic mechanisms. We also did not record actual adverse drug events in the patients, which is an issue that would be ideally pursued further in a longitudinal study. Thus, additional studies are warranted to examine how pDDI resources can be better integrated in routine clinical practice to provide a quick overview on unwanted effects and serious problems related to inappropriate drug use in MS

patients. In the future, patient safety might be improved by machine learning methods, which can help in predicting relevant interactions between multiple drugs (Basile et al., 2019; Han et al., 2022). Further research might also involve the patients and investigate whether they are aware of the problem and understand information about pDDIs (Hammar et al., 2021).

In conclusion, our study provides a comprehensive comparison of the three pDDI screening tools Stockley's, Drugs.com and MediQ based on a sample of 627 patients. A total of 1,684 different pDDIs were identified, with large differences between the databases in the number of pDDIs recorded (range: 706–1,161). Due to the heterogeneity in the classification of pDDI severities, only six of the 336 different severe pDDIs were rated as such in all three databases. In our patient cohort, citalopram was the drug most frequently involved in different severe pDDIs. Overall, 35.2% of the 627 patients had at least one severe pDDI, the occurrence of which was significantly associated with older age, lower educational level, living without a partner, comorbidities and the number of medications taken. In the context of chronic diseases such as MS, polypharmacy and the assessment of pDDIs present major challenges that could be better addressed through improved digital health solutions. When searching for pDDIs, it is currently recommended to check more than one database to increase sensitivity. Periodic medication reviews by the treating physicians and appropriate reductions or substitutions of medications can reduce the risk of severe pDDIs and improve the therapy management.

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the ethics committees of the University of Rostock and of the State Medical Association of Thuringia. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MH, NF and UKZ conceptualized the study. NF, PB, JD, PM, SL, JB, BS and FH collected the data. MH analyzed the data and prepared the figures and tables. PB, JD and M-CH have verified the underlying data. MH, NF, PB, JD and M-CH interpreted the data and drafted the original manuscript. UKZ supervised the research and provided important intellectual

content. All authors have read and approved the final version of the manuscript.

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Conflict of interest

MH received speaking fees and travel funds from Bayer HealthCare, Biogen, Merck Serono, Novartis and Teva. NF received travel funds for research meetings from Novartis. UKZ received speaking fees, travel support and/or financial support for research activities from Alexion, Almirall, Bayer, Biogen, Janssen, Merck Serono, Novartis, Octapharm, Roche, Sanofi Genzyme, Teva as well as EU, BMBF, BMWi and DFG.

The remaining 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.

References

- Abrantes, F. F., Moraes, M. P. M., Albuquerque Filho, J. M. V., Alencar, J. M. D., Lopes, A. B., Pinto, W. B. V. R., et al. (2021). Immunosuppressors and immunomodulators in Neurology - Part I: a guide for management of patients under immunotherapy. *Arq. Neuropsiquiatr.* 79 (11), 1012–1025. doi:10.1590/0004-282X-ANP-2020-0593
- Aburto, J. M., Villavicencio, F., Basellini, U., Kjærgaard, S., and Vaupel, J. W. (2020). Dynamics of life expectancy and life span equality. *Proc. Natl. Acad. Sci. U. S. A.* 117 (10), 5250–5259. doi:10.1073/pnas.1915884117
- Adam, T. J., and Vang, J. (2015). Content and usability evaluation of patient oriented drug-drug interaction websites. *AMIA Annu. Symp. Proc.* 2015, 287–296.
- Akaike, H. (2011). "Akaike's information criterion," in *International Encyclopedia of Statistical Science*. Editor M. Lovric (Berlin, Heidelberg: Springer). doi:10.1007/978-3-642-04898-2_110
- Amkreutz, J., Koch, A., Buendgens, L., Trautwein, C., and Eisert, A. (2017). Clinical decision support systems differ in their ability to identify clinically relevant drug interactions of immunosuppressants in kidney transplant patients. *J. Clin. Pharm. Ther.* 42 (3), 276–285. doi:10.1111/jcpt.12508
- Anglin, R., Yuan, Y., Moayyedi, P., Tse, F., Armstrong, D., Leontiadis, G. I., et al. (2014). Risk of upper gastrointestinal bleeding with selective serotonin reuptake inhibitors with or without concurrent nonsteroidal anti-inflammatory use: a systematic review and meta-analysis. *Am. J. Gastroenterol.* 109 (6), 811–819. doi:10.1038/ajg.2014.82
- Apel-Neu, A., and Zettl, U. K. (2008). Complementary and alternative medicine in multiple sclerosis. *J. Neurol.* 255 (Suppl. 6), 82–86. doi:10.1007/s00415-008-6015-9
- Armahizer, M. J., Kane-Gill, S. L., Smithburger, P. L., Anthes, A. M., and Seybert, A. L. (2013). Comparing drug-drug interaction severity ratings between bedside clinicians and proprietary databases. *ISRN Crit. Care* 2013, 1–6. doi:10.5402/2013/347346
- Arvin, A. M., Wolinsky, J. S., Kappos, L., Morris, M. I., Reder, A. T., Tornatore, C., et al. (2015). Varicella-zoster virus infections in patients treated with fingolimod: risk assessment and consensus recommendations for management. *JAMA Neurol.* 72 (1), 31–39. doi:10.1001/jamaneurol.2014.3065
- Bachmann, P., Frahm, N., Debus, J. L., Mashhadiakbar, P., Langhorst, S. E., Streckenbach, B., et al. (2022). Prevalence and severity of potential drug-drug interactions in patients with multiple sclerosis with and without polypharmacy. *Pharmaceutics* 14 (3), 592. doi:10.3390/pharmaceutics14030592
- Bar-Or, A., and Li, R. (2021). Cellular immunology of relapsing multiple sclerosis: Interactions, checks, and balances. *Lancet. Neurol.* 20 (6), 470–483. doi:10.1016/S1474-4422(21)00063-6
- Basile, A. O., Yahi, A., and Tatonetti, N. P. (2019). Artificial intelligence for drug toxicity and safety. *Trends Pharmacol. Sci.* 40 (9), 624–635. doi:10.1016/j.tips.2019.07.005
- Bayas, A., Schuh, K., Baier, M., Vormfelde, S. V., and REGAIN Study Group. (2016). Combination treatment of fingolimod with antidepressants in relapsing-remitting multiple sclerosis patients with depression: a multicentre, open-label study - REGAIN. *Ther. Adv. Neurol. Disord.* 9 (5), 378–388. doi:10.1177/1756285616651197
- Bechtold, B., and Clarke, J. (2021). Multi-factorial pharmacokinetic interactions: Unraveling complexities in precision drug therapy. *Expert Opin. Drug Metab. Toxicol.* 17 (4), 397–412. doi:10.1080/17425255.2021.1867105
- Behr, E. R., and Roden, D. (2013). Drug-induced arrhythmia: pharmacogenomic prescribing? *Eur. Heart J.* 34 (2), 89–95. doi:10.1093/eurheartj/ehs351
- Bermel, R. A., Hashmonay, R., Meng, X., Randhawa, S., von Rosenstiel, P., Sfikas, N., et al. (2015). Fingolimod first-dose effects in patients with relapsing multiple sclerosis concomitantly receiving selective serotonin-reuptake inhibitors. *Mult. Scler. Relat. Disord.* 4 (3), 273–280. doi:10.1016/j.msard.2015.04.002
- Bogetti-Salazar, M., González-González, C., Juárez-Cedillo, T., Sánchez-García, S., and Rosas-Carrasco, O. (2016). Severe potential drug-drug interactions in older adults with dementia and associated factors. *Clin. (Sao Paulo)* 71 (1), 17–21. doi:10.6061/clinics/2016(01)04
- Boström, I., Stawiarz, L., and Landtblom, A. M. (2013). Sex ratio of multiple sclerosis in the National Swedish MS Register (SMSreg). *Mult. Scler.* 19 (1), 46–52. doi:10.1177/1352458512446169

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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.2022.946351/full#supplementary-material>

SUPPLEMENTAL FIGURE S1

Network visualization of severe potential drug-drug interactions detected in patients with multiple sclerosis. A total of 1,684 different pDDIs were recorded for the 627 patients in this study. This graph shows a subset of 336 pDDIs that were classified as severe in at least one of the three databases used. The interactions (edges) connect 164 different active drug ingredients (nodes), including 7 DMDs for MS. The size of the nodes corresponds to the number of different pDDIs in which the drug is involved. The thickness of the edges indicates the frequency of the pDDIs in the patient cohort. The color of the edges indicates the consistency of the severity rating across the databases. DMD, disease-modifying drug; MS, multiple sclerosis; pDDI, potential drug-drug interaction.

- Bray, J. J. H., and Hancox, J. C. (2017). Solifenacin linked QT interval prolongation and torsades de pointes. *Ther. Adv. Drug Saf.* 8 (7), 245–247. doi:10.1177/2042098617702616
- Chen, H., and Boutros, P. C. (2011). VennDiagram: a package for the generation of highly-customizable venn and euler diagrams in R. *BMC Bioinforma.* 12, 35. doi:10.1186/1471-2105-12-35
- Chen, X. P., Tan, Z. R., Huang, S. L., Huang, Z., Ou-Yang, D. S., Zhou, H. H., et al. (2003). Isozyme-specific induction of low-dose aspirin on cytochrome P450 in healthy subjects. *Clin. Pharmacol. Ther.* 73 (3), 264–271. doi:10.1067/mcp.2003.14
- Dargahi, N., Katsara, M., Tselios, T., Androutsou, M. E., de Courten, M., Matsoukas, J., et al. (2017). Multiple sclerosis: Immunopathology and treatment update. *Brain Sci.* 7 (7), 78. doi:10.3390/brainsci7070078
- Debus, J. L., Bachmann, P., Frahm, N., Mashhadiakbar, P., Langhorst, S. E., Streckenbach, B., et al. (2022). Associated factors of potential drug-drug interactions and drug-food interactions in patients with multiple sclerosis. *Ther. Adv. Chronic Dis.* 13, 20406223221108391. doi:10.1177/20406223221108391
- Desta, Z., Soukhova, N. V., and Flockhart, D. A. (2001). Inhibition of cytochrome P450 (CYP450) isoforms by isoniazid: potent inhibition of CYP2C19 and CYP3A. *Antimicrob. Agents Chemother.* 45 (2), 382–392. doi:10.1128/AAC.45.2.382-392.2001
- Evans, E., Piccio, L., and Cross, A. H. (2018). Use of vitamins and dietary supplements by patients with multiple sclerosis: a review. *JAMA Neurol.* 75 (8), 1013–1021. doi:10.1001/jamaneurol.2018.0611
- Filippi, M., Bar-Or, A., Piehl, F., Preziosa, P., Solari, A., Vukusic, S., et al. (2018). Multiple sclerosis. *Nat. Rev. Dis. Prim.* 4 (1), 43. doi:10.1038/s41572-018-0041-4
- Frahm, N., Hecker, M., Langhorst, S. E., Mashhadiakbar, P., Haker, M. C., Zettl, U. K., et al. (2020a). The risk of polypharmacy, comorbidities and drug-drug interactions in women of childbearing age with multiple sclerosis. *Ther. Adv. Neurol. Disord.* 13, 1756286420969501. doi:10.1177/1756286420969501
- Frahm, N., Hecker, M., and Zettl, U. K. (2019). Multi-drug use among patients with multiple sclerosis: a cross-sectional study of associations to clinicodemographic factors. *Sci. Rep.* 9 (1), 3743. doi:10.1038/s41598-019-40283-5
- Frahm, N., Hecker, M., and Zettl, U. K. (2020b). Polypharmacy among patients with multiple sclerosis: a qualitative systematic review. *Expert Opin. Drug Saf.* 19 (2), 139–145. doi:10.1080/14740338.2020.1720646
- Francis, G., Kappos, L., O'Connor, P., Collins, W., Tang, D., Mercier, F., et al. (2014). Temporal profile of lymphocyte counts and relationship with infections with fingolimod therapy. *Mult. Scler.* 20 (4), 471–480. doi:10.1177/1352458513500551
- Fung, K. W., Kapusnik-Uner, J., Cunningham, J., Higby-Baker, S., and Bodenreider, O. (2017). Comparison of three commercial knowledge bases for detection of drug-drug interactions in clinical decision support. *J. Am. Med. Inf. Assoc.* 24 (4), 806–812. doi:10.1093/jamia/ocx010
- Hahn, M., and Roll, S. C. (2018). Validation of interaction databases in psychopharmacotherapy. *Nervenarzt* 89 (3), 319–326. doi:10.1007/s00115-017-0385-0
- Hammar, T., Hamqvist, S., Zetterholm, M., Jokela, P., and Ferati, M. (2021). Current knowledge about providing drug-drug interaction services for patients-A scoping review. *Pharm. (Basel)* 9 (2), 69. doi:10.3390/pharmacy9020069
- Han, K., Cao, P., Wang, Y., Xie, F., Ma, J., Yu, M., et al. (2022). A review of approaches for predicting drug-drug interactions based on machine learning. *Front. Pharmacol.* 12, 814858. doi:10.3389/fphar.2021.814858
- Hauser, S. L., and Cree, B. A. C. (2020). Treatment of multiple sclerosis: a review. *Am. J. Med.* 133 (12), 1380–1390. e2. doi:10.1016/j.amjmed.2020.05.049
- Hiemke, C., Bergemann, N., Clement, H. W., Conca, A., Deckert, J., Domschke, K., et al. (2018). Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: Update 2017. *Pharmacopsychiatry* 51 (01/02), 9–62. doi:10.1055/s-0043-116492
- Hines, L. E., Malone, D. C., and Murphy, J. E. (2012). Recommendations for generating, evaluating, and implementing drug-drug interaction evidence. *Pharmacotherapy* 32 (4), 304–313. doi:10.1002/j.1875-9114.2012.01024.x
- Hughes, J. E., Russo, V., Walsh, C., Menditto, E., Bennett, K., Cahir, C., et al. (2021). Prevalence and factors associated with potential drug-drug interactions in older community-dwelling adults: a prospective cohort study. *Drugs Aging* 38 (11), 1025–1037. doi:10.1007/s40266-021-00898-8
- Kappos, L., D'Souza, M., Lechner-Scott, J., and Lienert, C. (2015). On the origin of Neurostatus. *Mult. Scler. Relat. Disord.* 4 (3), 182–185. doi:10.1016/j.msard.2015.04.001
- Kheshti, R., Aalipour, M., and Namazi, S. (2016). A comparison of five common drug-drug interaction software programs regarding accuracy and comprehensiveness. *J. Res. Pharm. Pract.* 5 (4), 257–263. doi:10.4103/2279-042X.192461
- Kochs, L., Wegener, S., Sühnel, A., Voigt, K., and Zettl, U. K. (2014). The use of complementary and alternative medicine in patients with multiple sclerosis: a longitudinal study. *Complement. Ther. Med.* 22 (1), 166–172. doi:10.1016/j.ctim.2013.11.006
- Koziolek, M., Alcaro, S., Augustijns, P., Basit, A. W., Grimm, M., Hens, B., et al. (2019). The mechanisms of pharmacokinetic food-drug interactions - a perspective from the UNGAP group. *Eur. J. Pharm. Sci.* 134, 31–59. doi:10.1016/j.ejps.2019.04.003
- Kurtzke, J. F. (1983). Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 33 (11), 1444–1452. doi:10.1212/wnl.33.11.1444
- Kusch, M. K., Haefeli, W. E., and Seidling, H. M. (2018). How to meet patients' individual needs for drug information - a scoping review. *Patient prefer. Adherence* 12, 2339–2355. doi:10.2147/PPA.S173651
- Larocca, N. G. (2011). Impact of walking impairment in multiple sclerosis: perspectives of patients and care partners. *Patient* 4 (3), 189–201. doi:10.2165/11591150-000000000-00000
- Lublin, F. D., Reingold, S. C., Cohen, J. A., Cutter, G. R., Sorensen, P. S., Thompson, A. J., et al. (2014). Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology* 83 (3), 278–286. doi:10.1212/WNL.0000000000000560
- Magyari, M., and Sorensen, P. S. (2020). Comorbidity in multiple sclerosis. *Front. Neurol.* 11, 851. doi:10.3389/fneur.2020.00851
- Maljuric, N. M., Noordam, R., Aarts, N., Niemeijer, M. N., van den Berg, M. E., Hofman, A., et al. (2015). Use of selective serotonin re-uptake inhibitors and the heart rate corrected QT interval in a real-life setting: the population-based rotterdam study. *Br. J. Clin. Pharmacol.* 80 (4), 698–705. doi:10.1111/bcp.12681
- Molokhia, M., and Majeed, A. (2017). Current and future perspectives on the management of polypharmacy. *BMC Fam. Pract.* 18 (1), 70. doi:10.1186/s12875-017-0642-0
- Monteith, S., and Glenn, T. (2019). A comparison of potential psychiatric drug interactions from six drug interaction database programs. *Psychiatry Res.* 275, 366–372. doi:10.1016/j.psychres.2019.03.041
- Monteith, S., Glenn, T., Gitlin, M., and Bauer, M. (2020). Potential drug interactions with drugs used for bipolar disorder: a comparison of 6 drug interaction database programs. *Pharmacopsychiatry* 53 (5), 220–227. doi:10.1055/a-1156-4193
- Niu, J., Straubinger, R. M., and Mager, D. E. (2019). Pharmacodynamic drug-drug interactions. *Clin. Pharmacol. Ther.* 105 (6), 1395–1406. doi:10.1002/cpt.1434
- Nochaiwong, S., Ruengorn, C., Awiphan, R., Chai-Adisaksotha, C., Tantraworasin, A., Phosuya, C., et al. (2022). Use of serotonin reuptake inhibitor antidepressants and the risk of bleeding complications in patients on anticoagulant or antiplatelet agents: a systematic review and meta-analysis. *Ann. Med.* 54 (1), 80–97. doi:10.1080/07853890.2021.2017474
- Ohle, L. M., Ellenberger, D., Flachenecker, P., Friede, T., Haas, J., Hellwig, K., et al. (2021). Chances and challenges of a long-term data repository in multiple sclerosis: 20th birthday of the German MS registry. *Sci. Rep.* 11 (1), 13340. doi:10.1038/s41598-021-92722-x
- Ostad Haji, E., Mann, K., Dragicevic, A., Müller, M. J., Boland, K., Rao, M. L., et al. (2013). Potential cost-effectiveness of therapeutic drug monitoring for depressed patients treated with citalopram. *Ther. Drug Monit.* 35 (3), 396–401. doi:10.1097/FTD.0b013e3182885d9d
- Patten, S. B., Marrie, R. A., and Carta, M. G. (2017). Depression in multiple sclerosis. *Int. Rev. Psychiatry* 29 (5), 463–472. doi:10.1080/09540261.2017.1322555
- Payne, R. A. (2016). The epidemiology of polypharmacy. *Clin. Med.* 16 (5), 465–469. doi:10.7861/clinmedicine.16-5-465
- Prely, H., Herledan, C., Caffin, A. G., Baudouin, A., Larbre, V., Maire, M., et al. (2022). Real-life drug-drug and herb-drug interactions in outpatients taking oral anticancer drugs: comparison with databases. *J. Cancer Res. Clin. Oncol.* 148 (3), 707–718. doi:10.1007/s00432-021-03645-z
- Preston, C. L. (2020). *Stockley's drug interactions*. 12th edition. London: Pharmaceutical Press.
- Ramos, G. V., Guaraldo, L., Japiassú, A. M., and Bozza, F. A. (2015). Comparison of two databases to detect potential drug-drug interactions between prescriptions of HIV/AIDS patients in critical care. *J. Clin. Pharm. Ther.* 40 (1), 63–67. doi:10.1111/jcpt.12222
- Repovic, P. (2019). Management of multiple sclerosis relapses. *Contin. (Minneapolis)* 25 (3), 655–669. doi:10.1212/CON.0000000000000739

- Roblek, T., Vaupotic, T., Mrhar, A., and Lainscak, M. (2015). Drug-drug interaction software in clinical practice: a systematic review. *Eur. J. Clin. Pharmacol.* 71 (2), 131–142. doi:10.1007/s00228-014-1786-7
- Rommer, P., and Zettl, U. K. (2022). Treatment options in multiple sclerosis and neuromyelitis optica spectrum disorders. *Curr. Pharm. Des.* 28 (6), 428–436. doi:10.2174/1381612827666210920151231
- Rommer, P. S., Eichstädt, K., Ellenberger, D., Flachenecker, P., Friede, T., Haas, J., et al. (2019a). Symptomatology and symptomatic treatment in multiple sclerosis: Results from a nationwide MS registry. *Mult. Scler.* 25 (12), 1641–1652. doi:10.1177/1352458518799580
- Rommer, P. S., König, N., Sühnel, A., and Zettl, U. K. (2018). Coping behavior in multiple sclerosis-complementary and alternative medicine: a cross-sectional study. *CNS Neurosci. Ther.* 24 (9), 784–789. doi:10.1111/cns.12857
- Rommer, P. S., Milo, R., Han, M. H., Satyanarayan, S., Sellner, J., Hauer, L., et al. (2019b). Immunological aspects of approved MS therapeutics. *Front. Immunol.* 10, 1564. doi:10.3389/fimmu.2019.01564
- Sancar, M., Kaşık, A., Okuyan, B., Batuhan, S., and Izzettin, F. V. (2019). Determination of potential drug-drug interactions using various software programs in a community pharmacy setting. *Turk. J. Pharm. Sci.* 16 (1), 14–19. doi:10.4274/tjps.30932
- Scherf-Clavel, O. (2022). Drug-drug interactions with over-the-counter medicines: Mind the unprescribed. *Ther. Drug Monit.* 44 (2), 253–274. doi:10.1097/FTD.0000000000000924
- Shannon, P., Markiel, A., Ozier, O., Baliga, N. S., Wang, J. T., Ramage, D., et al. (2003). Cytoscape: A software environment for integrated models of biomolecular interaction networks. *Genome Res.* 13 (11), 2498–2504. doi:10.1101/gr.1239303
- Shariff, A., Belagodu Sridhar, S., Abdullah Basha, N. F., Bin Taleth Alshemeil, S. S. H., and Ahmed Aljallaf Alzaabi, N. A. (2021). Assessing consistency of drug-drug interaction-related information across various drug information resources. *Cureus* 13 (3), e13766. doi:10.7759/cureus.13766
- Sheikh-Taha, M., and Asmar, M. (2021). Polypharmacy and severe potential drug-drug interactions among older adults with cardiovascular disease in the United States. *BMC Geriatr.* 21 (1), 233. doi:10.1186/s12877-021-02183-0
- Smithburger, P. L., Kane-Gill, S. L., and Seybert, A. L. (2010). Drug-drug interactions in cardiac and cardiothoracic intensive care units: an analysis of patients in an academic medical centre in the US. *Drug Saf.* 33 (10), 879–888. doi:10.2165/11532340-000000000-00000
- Smithburger, P. L., Kane-Gill, S. L., and Seybert, A. L. (2012). Drug-drug interactions in the medical intensive care unit: an assessment of frequency, severity and the medications involved. *Int. J. Pharm. Pract.* 20 (6), 402–408. doi:10.1111/j.2042-7174.2012.00221.x
- Stamoula, E., Sifas, S., Dardalas, I., Ainaizoglou, A., Matsas, A., Athanasiadis, T., et al. (2021). Antidepressants on multiple sclerosis: a review of *in vitro* and *in vivo* models. *Front. Immunol.* 12, 677879. doi:10.3389/fimmu.2021.677879
- Suriyakorn, B., Chairat, P., Boonyoprakarn, S., Rojanarattanangkul, P., Pisetchep, W., Hunsakunachai, N., et al. (2019). Comparison of potential drug-drug interactions with metabolic syndrome medications detected by two databases. *PLoS One* 14 (11), e0225239. doi:10.1371/journal.pone.0225239
- Suter, K., Waldner-Knogler, K., and Sirot, E. J. (2013). mediQ—Ein Interaktionsprogramm für mehr Medikamentensicherheit. *Pipette-Swiss Lab. Med.* 6, 17–18.
- Tannenbaum, C., and Sheehan, N. L. (2014). Understanding and preventing drug-drug and drug-gene interactions. *Expert Rev. Clin. Pharmacol.* 7 (4), 533–544. doi:10.1586/17512433.2014.910111
- Tecen-Yucel, K., Bayraktar-Ekincioglu, A., Yildirim, T., Yilmaz, S. R., Demirkan, K., Erdem, Y., et al. (2020). Assessment of clinically relevant drug interactions by online programs in renal transplant recipients. *J. Manag. Care Spec. Pharm.* 26 (10), 1291–1296. doi:10.18553/jmcp.2020.26.10.1291
- Theroux, P., Ouimet, H., McCans, J., Latour, J. G., Joly, P., Lévy, G., et al. (1988). Aspirin, heparin, or both to treat acute unstable angina. *N. Engl. J. Med.* 319 (17), 1105–1111. doi:10.1056/NEJM198810273191701
- Thompson, A. J., Banwell, B. L., Barkhof, F., Carroll, W. M., Coetzee, T., Comi, G., et al. (2018). Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet. Neurol.* 17 (2), 162–173. doi:10.1016/S1474-4422(17)30470-2
- van Rey, F., and Heesakkers, J. (2011). Solifenacin in multiple sclerosis patients with overactive bladder: a prospective study. *Adv. Urol.* 2011, 834753. doi:10.1155/2011/834753
- Vonbach, P., Dubied, A., Krähenbühl, S., and Beer, J. H. (2008). Evaluation of frequently used drug interaction screening programs. *Pharm. World Sci.* 30 (4), 367–374. doi:10.1007/s11096-008-9191-x
- Walton, C., King, R., Rechtman, L., Kaye, W., Leray, E., Marrie, R. A., et al. (2020). Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition. *Mult. Scler.* 26 (14), 1816–1821. doi:10.1177/1352458520970841
- Wang, L. M., Wong, M., Lightwood, J. M., and Cheng, C. M. (2010). Black box warning contraindicated comedications: concordance among three major drug interaction screening programs. *Ann. Pharmacother.* 44 (1), 28–34. doi:10.1345/aph.1M475
- Weih, M., Roßnagel, F., Dikow, H., Wehrle, K., Braune, S., Bergmann, A., et al. (2020). Data on multiple sclerosis in Germany and their representation in the ambulatory registry NeuroTransData (NTD) network. *Fortschr. Neurol. Psychiatr.* 88 (6), 379–385. doi:10.1055/a-1130-6222
- Weingart, S. N., Toth, M., Sands, D. Z., Aronson, M. D., Davis, R. B., Phillips, R. S., et al. (2003). Physicians' decisions to override computerized drug alerts in primary care. *Arch. Intern. Med.* 163 (21), 2625–2631. doi:10.1001/archinte.163.21.2625
- Wickham, H. (2016). *ggplot2: Elegant graphics for data analysis*. 2nd edition. New York: Springer.
- Winkelmann, A., Loebermann, M., Barnett, M., Hartung, H. P., and Zettl, U. K. (2022). Vaccination and immunotherapies in neuroimmunological diseases. *Nat. Rev. Neurol.* 18 (5), 289–306. doi:10.1038/s41582-022-00646-5
- Winkelmann, A., Loebermann, M., Reisinger, E. C., Hartung, H. P., and Zettl, U. K. (2016). Disease-modifying therapies and infectious risks in multiple sclerosis. *Nat. Rev. Neurol.* 12 (4), 217–233. doi:10.1038/nrneuro.2016.21
- Zanghi, A., D'Amico, E., Lo Fermo, S., and Patti, F. (2021). Exploring polypharmacy phenomenon in newly diagnosed relapsing-remitting multiple sclerosis: a cohort ambispective single-centre study. *Ther. Adv. Chronic Dis.* 12, 2040622320983121. doi:10.1177/2040622320983121
- Zettl, U. K., Stüve, O., and Patejdl, R. (2012). Immune-mediated CNS diseases: a review on nosological classification and clinical features. *Autoimmun. Rev.* 11 (3), 167–173. doi:10.1016/j.autrev.2011.05.008

9. Anhang

9.1. Abkürzungsverzeichnis

Abb.	Abbildung
ADR	<i>adverse drug reactions</i> , unerwünschte Arzneimittelwirkungen
bspw.	beispielsweise
bzw.	beziehungsweise
ca.	circa
CDSS	<i>clinical decision support software</i> , Software zur klinischen Entscheidungsfindung
CI	<i>confidence interval</i> , Konfidenzintervall
CIS	<i>clinically isolated syndrome</i> , klinisch isoliertes Syndrom
DALY	<i>disability-adjusted life years</i> , krankheitsbelastete Lebensjahre
DDI	<i>drug-drug interaction</i> , Medikamenteninteraktion
DDID	<i>drug-drug interaction database</i> , Medikamenteninteraktionsdatenbank
d. h.	das heißt
DMD	<i>disease-modifying drug</i> , Verlaufsmodifizierendes Medikament
DMSG	Deutsche Multiple Sklerose Gesellschaft
EDSS	<i>Expanded Disability Status Scale</i>
HLA	humanes Leukozytenantigen
Kap.	Kapitel
MS	Multiple Sklerose
MW	Mittelwert
<i>n</i>	Anzahl
OR	<i>odds ratio</i> , Chancenverhältnis
OTC	<i>over-the-counter</i> , nicht verschreibungspflichtig
<i>p</i>	p-Wert
PD	Pharmakodynamik
pDDI	<i>potential drug-drug interaction</i> , potenzielle Medikamenteninteraktion

pDFI	<i>potential drug-food interaction</i> , potenzielle Nahrungsmittel-Medikamenteninteraktion
PK	Pharmakokinetik
PP	Polypharmazie
PPMS	<i>primary progressive multiple sclerosis</i> , primär progrediente Multiple Sklerose
p. P.	pro Patient
PwP	<i>patients with polypharmacy</i> , Patienten mit Polypharmazie
Pw/oP	<i>patients without polypharmacy</i> , Patienten ohne Polypharmazie
RIS	radiologisch isoliertes Syndrom
RKI	Robert-Koch-Institut
RRMS	<i>relapsing-remitting multiple sclerosis</i> , schubförmig remittierende Multiple Sklerose
Rx	verschreibungspflichtiges Medikament
SA	Standardabweichung
sog.	sogenannt
SPMS	<i>secondary progressive multiple sclerosis</i> , sekundär progrediente Multiple Sklerose
Stockley's	Stockley's Interactions Checker
u. a.	unter anderem
vs.	versus
z. B.	zum Beispiel
ZNS	zentrales Nervensystem

9.2. Thesen zur Dissertation

1. Die Multiple Sklerose (MS) ist eine immunmedierte, neurodegenerative Erkrankung, die weltweit mehr als 2,8 Millionen Menschen betrifft und durch chronisch-entzündliche Prozesse das zentrale Nervensystem (ZNS) schädigt.
2. Zu den häufigsten der individuell sehr heterogenen Symptome gehören die Visusstörungen, Paresen, Dysästhesien sowie Blasen- und Mastdarmstörungen und neuropsychiatrische Symptome.
3. Oft ist eine hohe Anzahl an Medikamenten nötig, um Patienten mit MS adäquat zu behandeln, darunter verlaufsmodifizierende Medikamente, Symptomtherapeutika und Komorbiditätentherapeutika.
4. Polypharmazie (PP) ist uneinheitlich definiert. Die am häufigsten verwendeten Definitionen sind die Einnahme von \geq fünf Medikamenten jeglicher Art (totale PP) beziehungsweise (bzw.) die Einnahme von \geq fünf verschreibungspflichtigen Medikamenten (Rx-PP).
5. PP ist vor allem für ältere, multimorbide Patienten relevant, aber auch für chronisch Erkrankte, wie etwa Patienten mit MS, die trotz ihres teilweise noch jungen Alters schon eine Vielzahl an Medikamenten einnehmen müssen.
6. PP stellt einen Risikofaktor für potenzielle Medikamenteninteraktionen (potential drug-drug interactions, pDDIs) dar. Patienten mit MS sind aufgrund der Einnahme einer Vielzahl an Medikamenten daher stark gefährdet, (schwere) pDDIs zu haben. pDDIs sowie deren Assoziation zu PP sind bei Patienten mit MS bislang weitgehend unerforscht.
7. In der vorliegenden Arbeit sollten die Prävalenz und die Schweregrade von pDDIs bei Patienten mit MS untersucht werden. Dabei wurden die Patienten nach totaler PP und Rx-PP in Subgruppen unterteilt. pDDIs wurden mithilfe von den drei Interaktionssoftwares MediQ, Drugs.com und Stockley's Interactions Checker ermittelt und eingeschätzt.
8. Zusätzlich wurden mögliche Medikamenten-Nahrungsmittelinteraktionen (potential drug-food interactions, pDFIs) ermittelt und die Datenbanken zur Detektion von pDDIs miteinander verglichen.
9. Die Studienpopulation bestand aus 627 Patienten mit MS. Jeder Patient nahm im Durchschnitt 5,3 Medikamente ein, wovon im Mittel 4,2 verschreibungspflichtig waren (78,7%).
10. Von den Patienten waren 53,3% von totaler PP bzw. 38,6% von Rx-PP betroffen. Patienten mit PP nahmen signifikant mehr Medikamente ein als Patienten ohne PP (7,8 versus 2,6 Medikamente pro Patient für totale PP; 8,5 versus 3,3 Medikamente pro Patient für Rx-PP).
11. Die Verwendung der drei unterschiedlichen Interaktionssoftwares zur Evaluierung von pDDIs zeigte, dass zwischen diesen hinsichtlich der Erkennung

von pDDIs eine große Diskordanz herrscht. In jeder Datenbank wurden pDDIs identifiziert, die in den anderen beiden nicht aufgeführt waren. Insgesamt wurden 1684 verschiedene pDDIs erfasst. Je nach Datenbank waren 0,9% (MediQ), 14,4% (Drugs.com) bzw. 35,4% (Stockley's) der pDDIs als schwer eingestuft. Nur 18,9% aller pDDIs wurden in jeder der drei Datenbanken detektiert.

12. Nur 3,3% der pDDIs wurden von allen Softwares mit demselben Schweregrad eingestuft. Die größte Konkordanz bestand zwischen Stockley's und Drugs.com mit 60,0% Übereinstimmung in den Schweregraden der pDDIs.
13. Mehr als zwei Drittel aller Patienten (70,3%) waren von mindestens einer pDDI jeglicher Schwere betroffen. Pro Patient wurden durchschnittlich 5,7 pDDIs, davon 0,9 schwere pDDIs, in mindestens einer der drei Datenbanken identifiziert. Patienten mit Rx-PP hatten durchschnittlich sogar mehr als 10 pDDIs.
14. Mehr als 20% aller detektierten pDDIs enthielten mindestens ein frei verkäufliches Medikament (over-the-counter, OTC). Dazu zählte auch die häufigste als schwer identifizierte pDDI bestehend aus Acetylsalicylsäure und Enoxaparin mit Acetylsalicylsäure als OTC-Medikament.
15. Risikofaktoren für das Auftreten mindestens einer schweren pDDI waren u. a. eine erhöhte Anzahl eingenommener Medikamente, ein höheres Alter und ein erhöhter Behinderungsgrad (je $p < 0,001$).
16. Als schwerwiegend eingestufte pDFIs wurden für 34 Wirkstoffe ermittelt, wovon 21 mit Alkohol wechselwirkten. Die pDFI aus Alkohol und Ibuprofen betraf bis zu 16,7% aller Patienten.
17. Um die klinische Relevanz von pDDIs bei Patienten mit MS besser einschätzen zu können, sollten in zukünftigen Studien longitudinale Daten zu klinisch manifesten unerwünschten Arzneimittelwirkungen erhoben werden.
18. Wichtig ist, medizinisches Personal und Patienten für pDDIs zu sensibilisieren. Neue sowie bestehende Medikationspläne sollten regelmäßig im Hinblick auf pDDIs aktualisiert und zur Vermeidung von PP und pDDIs auf möglicherweise abzusetzende oder auszutauschende Präparate untersucht und optimiert werden.

9.3. Selbstständigkeitserklärung

Hiermit erkläre ich, die vorliegende Dissertation selbstständig und ohne unerlaubte Hilfe verfasst zu haben. Ich versichere, dass ich ausschließlich die angegebenen Quellen und Hilfsmittel verwendet habe. Die Regeln zur Sicherung guter wissenschaftlicher Praxis wurden beachtet. Die Arbeit wurde nie zuvor einer anderen Prüfungsbehörde vorgelegt.

Ort, Datum

Paula Bachmann

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09/2016 – 07/2017

Au-Pair-Jahr (Paris, Frankreich)