Aus der Klinik für Neurologie der Universitätsmedizin Rostock

Sektion: Neuroimmunologie

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Aspekte der Therapiesicherheit bei Patienten mit Multipler Sklerose: Polypharmazie, Medikamenteninteraktionen und unerwünschte Wirkungen auf die pränatale Entwicklung

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Die in dieser Arbeit aus Gründen der besseren Lesbarkeit verwendete männliche Form bezieht sich gleichermaßen auf das weibliche und anderweitige Geschlechtsidentitäten.

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1. Einleitung

Die Multiple Sklerose (MS) ist eine chronisch-immunvermittelte Erkrankung des zentralen Nervensystems (ZNS) mit weltweit steigender Inzidenz [1]. Im Verlauf der MS zeigen sich vielfältige Symptome, wie Paresen, Spastiken oder Störungen des Vegetativums, die adäquate Therapiestrategien erfordern. Die Erkrankung ist die häufigste Ursache für neurologische Behinderung im jungen Erwachsenenalter mit bleibenden Defiziten [2].

Die vorliegende Arbeit beschäftigt sich mit der Bedeutung von Polypharmazie, potenziellen Medikamenteninteraktionen (potential drug-drug interactions, pDDI), potenziellen Nahrungsmittelinteraktionen (drug-food interactions, pDFI) sowie dem pränatal schädlichen Potenzial von Medikamenten bei Patientinnen im gebärfähigen Alter mit MS anhand der Analyse von Medikationsplänen mit verschiedenen Datenbanken.

1.1. Einführung in das Krankheitsbild Multiple Sklerose

Weltweit sind rund 2,8 Millionen Menschen von MS betroffen [3]. Dabei zeigt sich eine steigende Prävalenz in den letzten Jahrzehnten (1990 vs. 2016: plus 10,4%) [4, 5]. Die MS wird meist im jungen Erwachsenalter diagnostiziert (20-40 Jahre), betrifft Frauen doppelt bis dreimal so häufig wie Männer und stellt in der Phase der Familienplanung eine besondere Herausforderung dar [2, 6, 7]. Ätiologisch ist ein komplexes Zusammenspiel von multiplen genetischen Faktoren, Umwelt- und Lebensstilfaktoren, wie Vitamin-D-Mangel, Epstein-Barr-Virus-Infektion, Rauchen und Übergewicht, bedeutsam [1, 5, 8]. Die MS wird in drei Verlaufsformen unterteilt: die schubförmig remittierende MS (RRMS), die sekundär progrediente MS (SPMS) und die primär progrediente MS (PPMS) [9]. Das klinisch-isolierte Syndrom (CIS) stellt ein initiales Stadium der MS dar, bei dem die Kriterien der räumlichen (z. B. radiologischer Nachweis weiterer Läsionen) oder zeitlichen (z. B. Schübe) Dissemination nach den überarbeiteten McDonald-Kriterien von 2017 noch nicht erfüllt sind [10].

1.2. Therapie der Multiplen Sklerose

Zur Behandlung der MS wird ein mehrdimensionales Therapieregime verwendet. Primär kommen immunmodulatorische Medikamente (disease-modifying drugs, DMD) zum Einsatz, die die Schubrate reduzieren und die Krankheitsprogression verzögern sollen [11, 12]. Zur akuten Schubtherapie wird in Deutschland vorrangig eine Hochdosis-Glucocorticoid-Therapie über 3-5 Tage durchgeführt [13]. Für die Behandlung MS-bedingter Symptome (z. B. Spastiken) werden Medikamente mit dem Ziel der Symptomreduktion eingesetzt [14]. Des Weiteren erfolgt die Behandlung von Komorbiditäten [15]. Außerdem nutzen viele Patienten

zusätzlich Präparate aus der Komplementär- und Alternativmedizin (CAM) oder Nahrungsergänzungsmittel (NEM) [16]. In einer deutschen Studie gaben 81,9% der befragten Patienten mit MS (PwMS) an, CAM zu nutzen [17].

1.3. Schwangerschaft unter MS-Therapie

Eine Schwangerschaft bei MS-Erkrankung unter DMD-Therapie sollte sorgfältig bedacht werden, da die meisten DMD während der Schwangerschaft kontraindiziert sind [18]. Bislang gibt es nur limitiert Daten zur sicheren Anwendung von DMD in der Schwangerschaft. Generell wird eine Unterbrechung der DMD-Therapie bereits vor der Konzeption empfohlen, um das Risiko für pränatale Schädigungen zu senken [19, 20]. Unter der Schwangerschaft nimmt die jährliche Schubrate (annualized relapse rate, ARR) vor allem im dritten Trimester ab, steigt postpartum jedoch wieder an [21, 22]. Bei Patienten mit hoher Krankheitsaktivität bzw. hoher ARR ist die Gabe von Interferon-beta (IFN-β) und Glatirameracetat (GA) sowie von Natalizumab bis zur 34. Schwangerschaftswoche potenziell gegeben [13, 23]. Bezüglich der symptomatischen Therapie (z. B. Spastiken) bei MS-Patientinnen gibt es Empfehlungen zur sicheren Therapie während der Schwangerschaft/Stillzeit [24]. Die pränatale Entwicklung umfasst im Folgenden sowohl die Embryonalphase (Befruchtung bis zur 8. Schwangerschaftswoche post conceptionem) als auch die Fetalphase (9. Schwangerschaftswoche post conceptionem bis zur Geburt) [25]. Aufgrund der oftmals unzureichenden Studienlage kann nur von potenziell pränatal toxischen Effekten gesprochen werden, weshalb die Anwendung von Medikamenten in der Schwangerschaft nicht empfohlen sind. Da ungeplante Schwangerschaften ein besonderes Risiko für eine pränatale Medikamentenexposition darstellen, ist eine sichere Kontrazeption unter DMD-Therapie wichtig [18, 26]. In Deutschland waren 29,4% der Schwangerschaften zwischen 1983 und 2020 unbeabsichtigt [27]. Aber auch die weiteren Therapiesäulen können das Risiko für eine potenziell pränatale Toxizität in der Schwangerschaft erhöhen. Bislang gibt es keine Kenntnisse über das Ausmaß, inwieweit Frauen mit MS im gebärfähigen Alter potenziell pränatal schädliche Medikamente einnehmen und über die Zuverlässigkeit von Empfehlungen aus entsprechenden Datenbanken.

1.4. Polypharmazie

Polypharmazie ist typischerweise als die gleichzeitige Einnahme von fünf oder mehr Präparaten definiert [28]. Während häufig bei älteren Patienten eine Polymedikation nachgewiesen werden kann, sind aufgrund der vielschichtigen Therapieindikationen bei der MS auch jüngere Erwachsene von Polypharmazie betroffen [29, 30]. Ein systematisches Review fand für PwMS eine Polypharmazierate von 15-59% [31]. In der Folge kann

Polypharmazie ursächlich für unerwünschte Arzneimittelwirkungen (UAW), vermehrte Hospitalisationen, physische und kognitive Beeinträchtigungen sowie geringere Therapieadhärenz sein [32, 33]. Bei PwMS sind multiple Faktoren bekannt, die mit einer höheren Polypharmaziewahrscheinlichkeit einhergehen z. B. ein geringer sozioökonomischer Status und eine höhere Anzahl an Komorbiditäten [34–37]. Die häufigste Arzneimittelgruppe, die bei PwMS zu Polypharmazie beiträgt, sind die bei Depressionen eingesetzten Antidepressiva (z. B. Citalopram) [34]. Bei PwMS ist die Prävalenz von Depressionen zwei- bis dreifach gegenüber der Allgemeinbevölkerung erhöht [38]. Insgesamt ist die Studienlage über Polypharmazie bei MS limitiert und weitere Forschungen sind essentiell, um insbesondere gesundheitliche Folgen durch unangemessene Pharmakotherapien zu ermitteln [29].

1.5. Potenzielle Medikamenteninteraktionen

Als pDDI sind pharmakodynamisch oder pharmakokinetisch (im Prozess der Freisetzung, Resorption, Verteilung, Metabolisierung oder Elimination auftretend) bedingte Wirkungsveränderungen an einem beteiligten Arzneimittel definiert, unabhängig davon, ob UAW auftreten [39, 40]. Hervorgerufen werden die Wechselwirkungen durch die gleichzeitige Medikamenteneinnahme [40]. In der Folge kann es zu einer Zu- oder Abnahme der Arzneimittelwirkung mit erhöhter Toxizität oder abgeschwächtem Wirkeffekt kommen [40]. Andererseits können pDDI auch synergistisch in einer Therapie genutzt werden (z. B. Levodopa und Decarboxylase-Hemmer) [41]. Schwere pDDI können zu lebensbedrohlichen Zuständen führen und/oder eine medizinische Intervention notwendig machen, z. B. aufgrund additiver ZNS-depressiver Wirkungen [42]. Ein geeignetes Therapiemanagement ist in Anbetracht zunehmender Gesundheitsrisiken durch pDDI im heutigen klinischen Alltag unerlässlich.

Aus ökonomischer Sicht entstehen durch die Behandlung von pDDI-bedingten UAW sowie damit assoziierte Hospitalisationen zusätzliche Kosten für das Gesundheitssystem [43]. Ein Anteil von 1-5% aller Hospitalisierungen steht mit pDDI und deren Folgen in Verbindung [44]. Daraus ergibt sich für Deutschland, dass rund 200.000-1.000.000 Patienten jährlich aufgrund von pDDI hospitalisiert werden [45]. Für PwMS mit mindestens einer pDDI (PmDDI) konnte ein durchschnittlich sieben Tage längerer Krankenhausaufenthalt im Vergleich zu PwMS ohne pDDI (PoDDI) nachgewiesen werden [43]. Bereits im Jahr 2011 betrugen die direkten (z. B. für medizinische Behandlungen) und indirekten Kosten (z. B. für Arbeitszeitausfall) durchschnittlich 6009€ für eine potenziell vermeidbare, medikamentenbedingte Hospitalisation in den Niederlanden [46]. In einem aktuelleren Review lagen die Kosten für

UAW-bedingte Hospitalisationen bei ambulanten Patienten zwischen 174-8515€ bzw. bei stationären Patienten mit einem durch UAW-bedingten verlängerten Krankenhausaufenthalt zwischen 2851-9015€ in den westlichen Ländern [47].

Um pDDI zu identifizieren stehen zahlreiche Screeningwerkzeuge zur Verfügung. Mithilfe der sogenannten drug-drug interaction databases (DDID) kann eine Risikobewertung der Arzneimitteltherapie durch medizinisches Personal und Patienten erfolgen. Bei einer Fülle von DDID (z. B. *Micromedex, Drug-Reax, Lexi-Interact*) [48] sollte der Anwender über Datenbanken und was es bei deren Anwendung zu beachten gilt, informiert sein. Bisherige Studien konnten nur einen geringen Übereinstimmungsgrad der identifizierten pDDI zwischen 5-44% bei den untersuchten Datenbanken finden [49–55]. Im Rahmen dieser Arbeit wurden drei DDID ausgewählt, um einen umfassenden Vergleich der paarweise analysierten pDDI durchzuführen. Die DDID wurden hinsichtlich der Zugangsmöglichkeit für Patienten *(Drugs.com)* und für medizinisches Fachpersonal *(MediQ)* sowie aufgrund einer jeweils hohen nachgewiesenen Sensivität ausgewählt [49, 56]. Die DDID Stockley´s ist aufgrund der Verwendung als Goldstandard in vorherigen Studien [49, 55] ausgesucht worden.

Obwohl die MS häufig mit einem komplexem Therapieregime behandelt wird, ist über das Ausmaß von pDDI bei PwMS wenig bekannt. Bisherige Studien zu pDDI beziehen sich u. a. auf andere Krankheitsbilder (z. B. Demenz) und umfassen ältere, multimorbide Patienten [42, 53, 57, 58]. Spezifische Studien zu pDDI bei MS beschäftigten sich mit dem Interaktionspotenzial einzelner Wirkstoffe (z. B. Natalizumab vs. IFN-β) [59] oder dem Einfluss einzelner Wirkstoffe auf die Enzymaktivität (z. B. Daclizumab vs. Cytochrom P450-Enzyme) [60]. Bekannt ist, dass klinisch relevante pDDI signifikant häufiger bei PwMS mit Polypharmazie (PmP) als bei PwMS ohne Polypharmazie (PoP) auftreten [35, 36]. Trotz der zunehmenden Aufmerksamkeit für Polypharmazie bei PwMS [29, 31, 34–36, 61] gab es zu Beginn dieser Arbeit keine Daten zum Ausmaß von pDDI bei PwMS unter Berücksichtigung aller Arzneimittel. Ziel der Arbeit war es, neues Wissen über häufige pDDI und assoziierte Faktoren bei PwMS im Rahmen einer großen, unselektierten MS-Kohorte zu erforschen. Durch neue Erkenntnisse zur Prävalenz und zum Schweregrad von pDDI bei PwMS kann die Therapiestrategie optimiert und UAW vermieden werden. Bei Frauen im gebärfähigen Alter mit MS wurde erstmals umfassend das potenzielle Risiko für pränatale Schäden durch Medikamente mithilfe von Datenbanken untersucht.

2. Fragestellungen

In Zeiten einer alternden und zunehmend multimorbiden Bevölkerung stellen pDDI eine pharmakologische, gesundheitliche und ökonomische Herausforderung dar. Insbesondere PwMS sind aufgrund des chronischen, heterogenen Krankheitsverlaufes mit einer vielschichtigen medikamentösen Therapie konfrontiert. Daraus resultiert ein erhöhtes Risiko für das Auftreten von pDDI. Mit der Kenntnis über pDDI und damit verbundenen Risikoprofilen von Patienten kann die MS-Therapie optimiert werden. Für Frauen im gebärfähigen Alter besteht ein besonderes Risiko, da die Einnahme von Medikamenten mit einer potenziellen Schwangerschaft interferieren und zu frühkindlichen Schädigungen führen kann. Das pränatale Risiko kann durch entsprechendes Wissen über gefährdende Arzneimittel und eine vorausschauende Therapieplanung vermindert werden. Für die im Rahmen dieser Arbeit durchgeführten Querschnittsuntersuchung wurden die Medikationspläne einer großen Studienpopulation von PwMS mithilfe von DDID auf pDDI untersucht. In einer Subpopulation von Frauen im gebärfähigen Alter wurde das Risiko für potenziell pränatal schädliche Medikamente während einer Schwangerschaft beleuchtet. Die Ergebnisse der Dissertationsarbeit fanden Eingang in drei Publikationen, die in der vorliegenden kumulativen Promotionsschrift zusammengefasst sind. Nachfolgend sind die Fragestellungen, die im Rahmen der Arbeit untersucht wurden, separat für die drei Publikationen aufgeführt.

Publikation 1: Associated factors of potential drug-drug interactions and drug-food interactions in patients with multiple sclerosis [62].

- Wie hoch ist die Prävalenz von pDDI in der untersuchten MS-Kohorte?
- In welchem Ausmaß ist Polypharmazie bei PwMS mit dem Auftreten von pDDI assoziiert?
- Unterscheiden sich PwMS mit mindestens einer pDDI in den soziodemographischen, klinischen und medikationsbezogenen Merkmalen von Patienten ohne pDDI?
- Welche schweren pDDI lassen sich in der MS-Kohorte am häufigsten finden und was gilt es für diese pDDI zu beachten?
- Wie viele potenzielle Nahrungsmittelinteraktionen (insgesamt und schwerwiegend) konnten unter den von der MS-Kohorte verwendeten Arzneimitteln gefunden werden?

Publikation 2: Screening for severe drug-drug interactions in patients with multiple sclerosis: a comparison of three drug interaction databases [63].

- Wie viele (schwere) pDDI gibt es im Durchschnitt pro MS-Patient?
- Welche Medikamente sind besonders häufig an schweren pDDI beteiligt?
- Welche soziodemographischen und klinischen Charakteristika von PwMS sind mit dem Auftreten von schweren pDDI assoziiert?
- Wie hoch ist der Übereinstimmungsgrad von drei verschiedenen DDID hinsichtlich der Detektionsrate von pDDI bei PwMS?
- Gibt es Unterschiede im Vergleich der DDID in der Bewertung der Schweregrade der identifizierten pDDI?

Publikation 3: Therapy of women with multiple sclerosis: an analysis of the use of drugs that may have adverse effects on the unborn child in the event of (unplanned) pregnancy [64].

- Hinsichtlich welcher klinischen und pharmakologischen Merkmale unterscheiden sich MS-Patientinnen, die Kontrazeptiva einnehmen, von MS-Patientinnen, die keine orale Kontrazeption nutzen?
- Unterscheiden sich die verwendeten Datenbanken hinsichtlich der Risikoeinschätzung für eine medikamentenassoziierte gestörte pränatale Entwicklung bei MS-Patientinnen?
- Wie hoch ist der Anteil von Frauen mit MS, die ein oder mehrere Medikamente einnehmen, die sich potenziell schädlich auf die pränatale Entwicklung auswirken?
- Wie häufig nehmen Patienten ohne Kontrazeption ein oder mehrere Medikamente ein, die nicht unter einer Schwangerschaft empfohlen sind?
- Welche häufig angewendeten Wirkstoffe von MS-Patientinnen wurden durch die Datenbanken als potenziell gefährlich für ein ungeborenes Kind eingeordnet?

3. Methoden

3.1. Studienpopulation

Grundlage der im Rahmen dieser Arbeit durchgeführten multizentrischen Querschnittsstudie bildet eine Studienkohorte von 627 PwMS. Im Rahmen der Untersuchung erfolgte zwischen März 2017 und Mai 2020 die Datenerhebung in der Klinik und Poliklinik für Neurologie der Universitätsmedizin Rostock und in der Neurologischen Klinik des Ökumenischen Hainich Klinikums Mühlhausen. Die Befragung der Patienten erfolgte während des stationären Aufenthalts oder vor der ambulanten Kontrolluntersuchung. In die Studie inkludiert wurden Patienten, die älter als 18 Jahre alt waren und die Diagnose einer MS oder eines CIS nach den aktuellen McDonald-Kriterien erfüllten [10]. Nicht eingeschlossen wurden minderjährige Patienten und solche ohne diagnostizierte MS oder CIS. Die Patienten erklärten ihre Teilnahme auf freiwilliger Basis durch schriftliche Einwilligung. Positive Ethikvoten lagen durch die Ethikkomitees der Universität Rostock und der Landesärztekammer Thüringen (Registriernummer A 2014-0089 und A 2019-0048) vor. Die Studie wurde entsprechend der Deklaration von Helsinki durchgeführt [65].

3.2. Datenerhebung und -einteilung

Die Datenerhebung erfolgte durch Anamnese, klinische Untersuchung, Patientenakteneinsicht und einem strukturierten Patienteninterview. Die erfassten Informationen wurden in drei Kategorien unterteilt: soziodemographische, klinische und pharmazeutische Daten (Abb. 1).

Unter den soziodemographischen Daten wurden patientenbezogene Angaben über Alter, Geschlecht, Beziehungsstatus, Arbeitsstatus, Schuljahre (ohne Ausbildung/ Studium), Bildungsstand, Anzahl von Kindern und Geschwistern sowie Wohnort (Stadt/Land) zusammengefasst. Zu den klinischen Daten zählten die Erkrankungsdauer der MS, der Krankheitsverlauf (CIS, RRMS, PPMS oder SPMS), der Behinderungsgrad nach der Expanded Disability Status Scale (EDSS) von Kurtzke [66] und die Anzahl und Art der Komorbiditäten neben der MS. Die pharmazeutischen Daten beinhalteten die Anzahl eingenommener Präparate pro Patient sowie Einnahmeintervall, Therapieziel und Verschreibungsstatus der Präparate. In dieser Untersuchung schließt der Begriff „Medikament“ sowohl Arzneimittel, als auch CAM und NEM ein.

Bezüglich des Einnahmeintervalls wurde zwischen einer Dauermedikation, die täglich oder in regelmäßigen Abständen eingenommen wird, und einer Bedarfsmedikation, deren Einnahme temporär oder im Notfall notwendig ist, unterschieden. Bei den Therapiezielen wurde die

verlaufsmodifizierende Behandlung der MS mit DMD, die Therapie von MS-begleitenden Symptomen (z. B. Spastik, Schmerz oder vegetative Dysfunktion) und die Behandlung von Komorbiditäten unterschieden. Zu den DMD wurde Methylprednisolon aufgrund des Einsatzes in der Schubtherapie [67] sowie bei der wiederholten Pulstherapie in fortgeschrittenen Stadien der MS gezählt [68]. Hinsichtlich des Zugangs erfolgte die Unterscheidung in verschreibungspflichtige (Rx) Präparate und freiverkäufliche (OTC) Medikamente (inklusive NEM und CAM). Zu beachten ist, dass verschreibungspflichtige Dosen durch die Kombination kleinerer Dosen freiverkäuflicher Medikamente zu erreichen sind (z. B. Ibuprofen). Auf dieser Grundlage wurde für jeden Patienten ein pseudonymisierter Medikationsplan in Microsoft Excel mit Informationen zu Präparat- und Wirkstoffnamen, Indikation, Wirkstärke, Dosierung und Applikationsform erstellt.

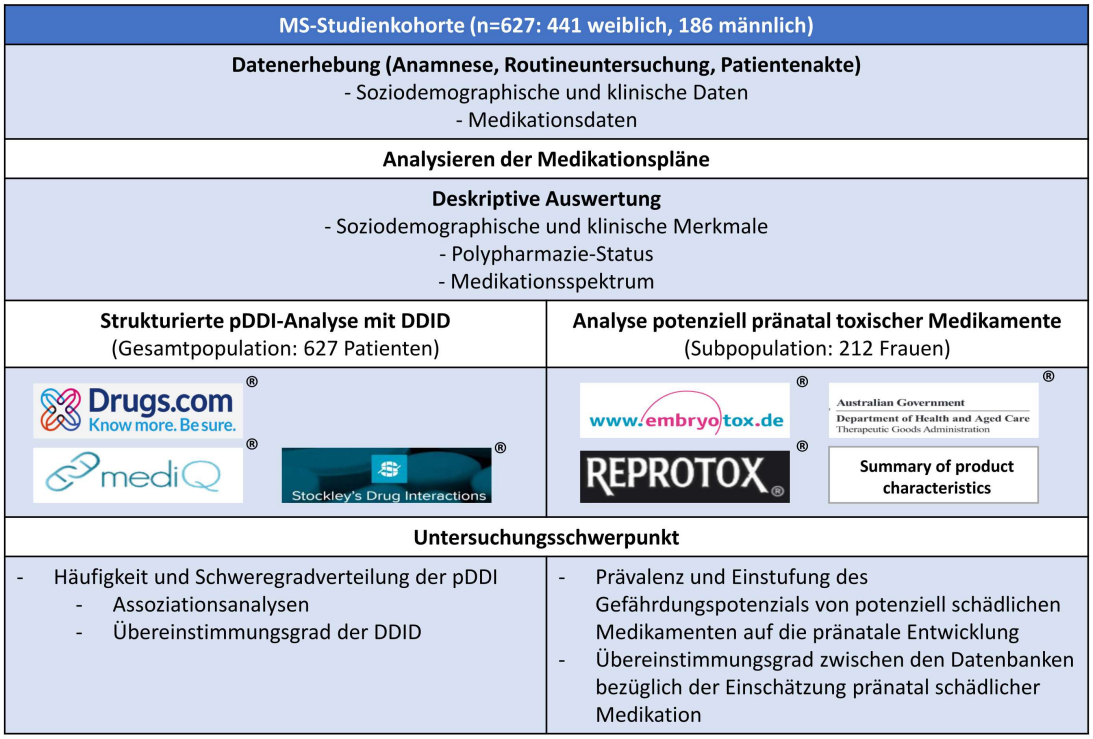

***Abb. 1: Studiendesign**. Zu 627 Patienten mit MS-/CIS-Diagnose wurden soziodemographische und klinische Daten erhoben und für jeden Patienten ein Medikationsplan erstellt. Im Rahmen der Untersuchung wurde von der Gesamtkohorte eine Subpopulation von 212 Frauen im gebärfähigen Alter gesondert betrachtet. Für die gesamte Studienpopulation und für die Untergruppe wurde eine deskriptive Auswertung der soziodemographischen und klinischen Merkmale, des Medikationsspektrums und des Polypharmazie-Status durchgeführt. Die Analyse der Gesamtkohorte auf pDDI erfolgte unter Verwendung von drei DDID: Drugs.com Drug Interaction Checker, MediQ und Stockley´s Interaction Checker. In der Subpopulation wurden potenziell pränatal schädliche Medikamente mithilfe von vier Ressourcen untersucht: Embryotox, Reprotox, TGA und SmPC.*

CIS: Klinisch isoliertes Syndrom; DDID: Arzneimittelinteraktionsdatenbanken; MS: Multiple Sklerose; pDDI: potenzielle Medikamenteninteraktionen; SmPC: Summary of medical product characteristics, TGA: Therapeutic Goods Administration.

3.3. Analyse der Arzneimittelinteraktionen mittels Datenbanken

Die Analyse von paarweisen pDDI erfolgte von Mai bis Oktober 2020 unter der Verwendung von drei DDID.

Drugs.com Drug Interaction Checker ist eine online verfügbare, englischsprachige Interaktionsdatenbank mit Informationen über 24.000 Medikamente. Neben Medikamentenwechselwirkungen (drug-drug) werden auch Interaktionen von Medikamenten mit Nahrungsmitteln/Getränken (drug-food/beverage) angezeigt. Die Website richtet sich in erster Linie an Patienten, jedoch ist auch ein Modus für medizinisches Personal verfügbar[69].

Stockley´s Interaction Checker ist ein abonnementpflichtiges, englischsprachiges Interaktionsprogramm, welches von der Royal Pharmaceutical Society herausgegeben wird. Es greift auf über 110.000 Arzneimittelinteraktionen mit Medikamenten (drug-drug), Nahrungsmitteln (drug-food/beverage), Tabak (drug-smoking) und Pflanzen (drug-herb) zurück. Die Zielgruppe umfasst v. a. medizinisches Personal [70].

MediQ ist eine kostenpflichtige DDID in deutscher Sprache mit mehr als 52.000 verfügbaren Interaktionen. Es gibt Informationen zu Interaktionen zwischen Medikamenten (drug-drug), Nahrungsmitteln (drug-food), Alkohol (drug-alcohol) und genetischen Polymorphismen (drug-polymorphism). Das System ist primär für Gesundheitsexperten gedacht [71].

Diese DDID unterteilen die Schweregrade einer pDDI jeweils in drei Kategorien: leichtgradig (Drugs.com: mild, MediQ: gering, Stockley´s: mild), moderat (moderate/ durchschnittlich/ moderate) und schwergradig (major/ hoch/ severe). In jedes der Interaktionsprogramme wurden die 627 Medikationspläne pseudonymisiert mit Präparat-, alternativ mit Wirkstoffnamen, eingegeben. Die aufgezeigten pDDI wurden anschliessend unter Angabe des Schweregrades mit den jeweiligen Wirkstoffen im Medikationsplan vermerkt.

Für Publikation 1 wurde im nächsten Schritt ein kombinierter Score anhand der Schweregrade der pDDI aus *Drugs.com* und *Stockley´s* berechnet. Zur Bildung des Scores erhielten die pDDI, je nach Schweregrad, einen einheitlich definierten Punktwert: 0 Punkte (kein Nachweis einer pDDI), 1 Punkt (leichte pDDI), 2 Punkte (moderate pDDI), drei Punkte (schwere pDDI). Durch Addition des Punktwertes der pDDI von einer DDID mit dem Punktwert der pDDI der zweiten DDID ergab sich ein neuer Wert zur Einschätzung des pDDI-Schweregrades in fünf Stufen (Tab. 1).

Gesamtpunktzahl	Schweregrad
≤ 2	Leicht
3	Leicht- moderat
4	Moderat
5	Moderat-schwer
6	schwer

Tab. 1: Schweregradeinteilung. *Einteilung des Schweregrades bei der Kombination zweier Datenbanken. Beispielsweise ergab sich für die Interaktion von Levodopa mit Baclofen bei Stockley´s eine schwere Interaktion (3 Punkte) und bei Drugs.com eine moderate Interaktion (2 Punkte). Dies führte nach der neuen Einteilung zu einer moderat-schweren Interaktion (5 Punkte).*

Zusätzlich wurden Interaktionen zwischen Medikamenten und Nahrungsmitteln in Publikation 1 [62] dargestellt. Der Begriff „Nahrungsmittel“ erfasst zum einen den Alkoholkonsum und das Zigarettenrauchen. Andererseits kann das Intervall zwischen Medikamenten- und Nahrungsmitteleinnahme Auslöser einer pDFI sein. Die Schweregradeinordnung erfolgte nach den identifizierten pDFI-Schweregraden der jeweiligen DDID. Im Falle eines nicht übereinstimmenden Schweregrades einer pDFI zwischen den beiden DDID wurde der jeweils höhere Schweregrad gewertet.

Eine Herausforderung stellte die Präparateingabe und -auswertung dar. Aufgrund uneinheitlicher Wirkstoffbezeichnungen in den Datenbanken sowie deutschen und englischen Begriffen war es notwendig, unterschiedliche Wirkstoffbezeichnungen in einer Synonym- und Übersetzungstabelle zusammenzuführen. Ein besonderes Augenmerk wurde auf eine einheitliche Formatierung und eine gewissenhafte Prüfung der Tabellen auf Tippfehler gelegt. Kombinationspräparate (z. B. Kontrazeptiva mit Ethinylestradiol und Levonorgestrel) wurden in ihre Wirkstoffe aufgeteilt. Des Weiteren stellte die Einordnung Cannabis-basierter Präparate eine Schwierigkeit dar. *Drugs.com* teilte jegliche Präparate (z. B. Sativex) in die Komponenten „Cannabidiol“ und „Dronabinol“ auf, während bei *Stockley´s* die Eingabe von Cannabis und speziellen Präparaten möglich war. *MediQ* unterschied zwischen „Cannabis geraucht“ und „Cannabis nicht geraucht“. Da viele PwMS Cannabis als Spray (Sativex®) einnahmen, welches u.a. Cannabidiol und Dronabinol enthält, wurde als Lösung, unabhängig von der Applikationsform, Cannabis in Form von Cannabidiol und Dronabinol in die DDID eingegeben.

3.4. Untersuchung von Arzneimittelrisiken bei Frauen im gebärfähigen Alter

In der dritten Publikation wurde eine Untergruppe von 212 Frauen mit MS hinsichtlich des Polypharmazievorkommens und des potenziellen Risikos pränataler Schädigungen durch Medikamentengebrauch unter einer Schwangerschaft detailliert untersucht. Die Altersgrenze lag bei 48 Jahren, da weltweit die meisten Frauen zwischen 49 und 52 Jahren in die Menopause kommen [72]. Als Kontrazeptiva wurde die Einnahme aller hormonell wirkenden oralen Präparate oder die Anwendung von Vaginalringen berücksichtigt. Die gezielte Analyse der Medikationspläne bezüglich der Arzneimittelsicherheit während einer Schwangerschaft erfolgte von Juni bis August 2020 unter Anwendung von vier Datenbanken: *Embryotox [73], Reprotox [74], Therapeutic Goods Administration (TGA) [75]* und die deutschen Fachinformationen *(summary of medical product characteristics, SmPC)*.

Embryotox beinhaltet als deutsche Datenbank evidenzbasierte Informationen zur Arzneimitteltherapiesicherheit von mehr als 400 Wirkstoffen in der Schwangerschaft und Stillzeit [73]. Als englischsprachige Plattform umfasst *Reprotox* Informationen zu mehr als 5000 Wirkstoffen auf Basis klinischer und experimenteller Studien [74]. Die Website des australischen Gesundheitsministeriums basiert auf Empfehlungen medizinischer und wissenschaftlicher Sachverständigen aufgrund verfügbarer Erkenntnisse [75]. Die deutschen Fachinformationen für das jeweilige Präparat wurden ergänzend für die Bewertung von potenziell pränatal schädlichen Medikamenten herangezogen. Ziel der Datenbanken ist es Informationen zur Arzneimitteltherapiesicherheit in der Schwangerschaft als Orientierungshilfe für in erster Linie medizinisches Fachpersonal zu präsentieren.

Es gilt zu beachten, dass jede Datenbank auf einer eigenen Risikostratifizierung basierte. Jedes Medikament wurde in die Datenbanken eingegeben und die Risikoeinstufung erfasst. Wirkstoffe mit einem potenziell schädlichen Einfluss auf die pränatale Entwicklung wurden entsprechenden Kategorien zugeordnet: *Embryotox*: rote Kategorie, *Reprotox*: Kategorie 3, *TGA*: Kategorie B3, C, D und X sowie *SmPC*: Kategorie 2, 3 und 4.

Nach der Analyse in den Datenbanken erfolgte eine Einteilung der Medikamente in folgende Kategorien:

(1) Es sind keine gesundheitsschädlichen Effekte auf den Embryo/Fetus oder das Neugeborene zu erwarten.
(2) Aufgrund der unzureichenden Datenlage kann eine Anwendung in der Schwangerschaft nicht empfohlen werden.
(3) Die Medikamente können die physiologische pränatale Entwicklung beeinträchtigen.

3.5. Statistische Analyse

Zur Datenaufbereitung und statistischen Auswertung wurden IBM SPSS Statistics 27.0, Microsoft Excel 2010 und R Version 3.6.0 verwendet. Im ersten Schritt erfolgte die deskriptive Auswertung der soziodemographischen, klinischen und pharmazeutischen Daten unter der Angabe absoluter und relativer Häufigkeiten. Zudem wurden Mittelwerte, Mediane, Standardabweichungen sowie Spannweiten (Minimum-Maximum) berechnet. In der vergleichenden Analyse wurden statistische Tests angewendet, um Untergruppen der Studienpopulation hinsichtlich Unterschieden in den Merkmalen (z. B. Alter oder Krankheitsdauer) zu untersuchen. Für metrische Merkmale (z. B. Alter, EDSS-Score) wurde der Zweistichproben-t-Test bzw. der Mann-Whitney-U-Test verwendet. Der Chi-Quadrat-Test sowie der exakte Test nach Fisher kamen bei kategorialen Variablen zum Einsatz (z. B. Geschlecht, Verlaufsform). Einfache und multivariable binär logistische Regressionsanalysen wurden für die Assoziationsanalysen soziodemographischer, klinischer und medikationsbezogener Daten mit dem Auftreten von mindestens einer (schweren) pDDI und damit zur Identifizierung von Prädiktoren für das Auftreten von pDDI angewendet. Dabei wurde der p-Wert, die Odds Ratio (OR) und das 95%-Konfidenzintervall bestimmt. Das Signifikanzniveau wurde auf α=0.05 gesetzt. Die OR gibt die relative Wahrscheinlichkeit für die Stärke der Assoziation zweier Variablen an (z. B. inwiefern ein Risikofaktor mit dem Auftreten von pDDI assoziiert ist) [76]. Zur Darstellung der Ergebnisse wurden Abbildungen mit Hilfe von Microsoft Excel 2010/ Professional 2016, Cytoscape Version 3.9.0 sowie den R Paketen VennDiagramm und corrplot erstellt. Nähere Informationen zur Methodik sind den jeweiligen Publikationen zu entnehmen (Kapitel 4 und 8).

4. Ergebnisse und Diskussionen der Einzelpublikationen

Nachfolgend werden die drei Originalarbeiten, die ausführlich in Kapitel 8 dargeboten werden, kurz zusammengefasst und jeweils erneut Hintergrund und Methodik erläutert, bevor die Ergebnisse beschrieben und diskutiert werden. Eine integrative Betrachtung der Studien findet sich im Anschluss in Kapitel 5.

4.1. Publikation 1: Associated factors of potential drug-drug interactions and drug-food interactions in patients with multiple sclerosis

Die MS ist eine facettenreiche Erkrankung des ZNS und erfordert die Behandlung vielfältiger Symptome und potenzieller Komorbiditäten. Durch die Verwendung zahlreicher Arzneimittel, NEM und CAM besteht für PwMS ein hohes Risiko für das Auftreten von pDDI und pDFI. Kenntnisse über pDDI bei PwMS können das Auftreten von UAW reduzieren und den Therapieerfolg entscheidend verbessern. Das Ziel dieser Arbeit war die Bestimmung der Häufigkeit und Schwere von pDDI und pDFI bei PwMS unter Beachtung des Aspektes der Polypharmazie (Einnahme von mindestens fünf Präparaten). Dazu wurden die Medikationspläne von 627 PwMS mit zwei DDID (*Drugs.com* und *Stockley´s*) hinsichtlich pDDI und pDFI unter Berücksichtigung des Schweregrads untersucht.

In der Untersuchungskohorte (n=627) fanden sich 334 (53,3%) PmP, die im Vergleich zu PoP (n=293) häufiger schwerwiegende pDDI aufwiesen (17,7% vs. 1,7%). In den univariaten Regressionsanalysen zeigte sich Polypharmazie als die am stärksten mit pDDI assoziierte Variable. Die Wahrscheinlichkeit für schwere pDDI bzw. pDDI jeglichen Schweregrades war unter Polypharmazie um das 15-fache bzw. 27-fache höher als bei PoP. In der gesamten Studienpopulation konnten 2587 pDDI detektiert werden (gezählt mit Wiederholungen). Während leichte pDDI (57,1%) den Großteil der gefundenen Interaktionen ausmachten, hatten schwerwiegende pDDI einen Anteil von 12,9% (moderat-schwere pDDI: 9,5%, schwere pDDI: 3,4%). Bei 408 Patienten (65,1%) konnte mindestens eine pDDI gefunden werden. PmDDI waren durchschnittlich 9 Jahre älter, 3 Jahre länger an MS erkrankt und hatten einen um 2 EDSS-Punkte höheren Behinderungsgrad als PoDDI. Die häufigste schwere pDDI konnte zwischen Citalopram und Fingolimod identifiziert werden (n=7 Patienten). Mit Acetylsalicylsäure und Ibuprofen konnten zwei der drei am häufigsten an schweren pDDI beteiligten Medikamente in der Gruppe der freiverkäuflichen Präparate gefunden werden. Insgesamt konnten 254 pDFI identifiziert werden, von denen 34 als schwerwiegend klassifiziert wurden. Alkohol war an 21 schweren pDFI beteiligt und damit das häufigste „Nahrungsmittel“ mit schweren pDFI.

Der Anteil von PmP in dieser Arbeit steht mit den Polypharmazieraten (14-77%) in der Literatur im Einklang [31, 34, 77]. Auch mit Polypharmazie assoziierte Patientencharakteristika (z. B. höheres Alter, mehrere Komorbiditäten) konnten bestätigt werden [34, 37]. Diese Arbeit verdeutlicht die starke Assoziation von Polypharmazie und dem Auftreten von (schweren) pDDI in einer unselektiven MS-Kohorte. Erstmals konnte neues Wissen zur Prävalenz und Schwere von pDDI bei PwMS generiert werden. Ähnliche Studien

zum Vorkommen von pDDI wurden bislang in anderen Patientenkohorten durchgeführt. Bei Demenzerkrankten wurde für 59,1% der Patienten mindestens eine pDDI detektiert [57, 58]. Prely *et al* konnten bei ambulanten Patienten mit oraler Krebstherapie bei 89,4% der Patienten eine oder mehrere pDDI finden [53]. Jedoch ist ein Vergleich der Studien aufgrund verschiedener Krankheitsentitäten, Einschlusskriterien und verwendeter DDID unzulässig. In der Literatur wurde die Analyse von pDDI bisher entweder mit Hilfe von einer DDID durchgeführt [57, 58] oder es wurden mehrere DDID [53] separat betrachtet, sodass die Bildung eines kombinierten Scores aus zwei DDID mit dem Ziel einer präziseren Vorhersage von pDDI eine weitere Besonderheit dieser Arbeit darstellt.

Ein Fokus dieser Arbeit lag explizit auf der Berücksichtigung von OTC-Präparaten und NEM. OTC-Präparate wie Ibuprofen werden aufgrund ihres weniger eingeschränkten Zuganges nicht selten eigenständig durch die Patienten verwendet. Dies birgt durch fehlende Absprache mit den behandelnden Ärzten die Gefahr für pDDI mit der verschriebenen Medikation. Daher sollte bei der ärztlichen Konsultation nach CAM und NEM gefragt werden, um mögliche Interaktionspartner nicht zu übersehen sowie um eine vollständige Medikamentenliste für die Berücksichtigung bei zukünftigen Verordnungen zu haben. Bereits vorherige Studien konnten die häufige Beteiligung von nichtsteroidalen Antirheumatika an OTC-pDDI nachweisen [78, 79]. Tachi *et al*. konnten bei Frauen einen höheren Einsatz von OTC-Medikamenten und NEM nachweisen als bei Männern [80]. Da 70,3% der untersuchten MS-Kohorte weiblich waren, sollte das Geschlecht als ein möglicher Faktor für die häufige Beteiligung von OTC-Präparaten an pDDI in Betracht gezogen werden.

Die häufigste schwerwiegende pDDI wurde zwischen Citalopram und Fingolimod gefunden. Dabei steigt mutmaßlich das kardiovaskuläre Risiko durch eine QT-Zeit verlängernde Wirkung des Citaloprams und ein erhöhtes Risiko für Bradyarrhythmien durch Fingolimod [81, 82]. In klinischen Studien konnte jedoch kein zusätzliches Risiko für pathologische elektrokardiographische Veränderungen bei Patienten mit kombinierter Gabe von Citalopram und Fingolimod gefunden werden, gegenüber Patienten ohne Citalopram [83, 84]. Eine kardiologische Überwachung innerhalb der ersten sechs Stunden nach der initialen Fingolimod-Gabe ist jedoch empfehlenswert [85].

Für klinisch relevante pDFI gibt es bislang nur eine begrenzte Anzahl wissenschaftlicher Studien und der überwiegende Teil an pDFI-Warnungen basiert auf den Empfehlungen der Medikamentenhersteller [86]. Um tatsächlich auftretende pDFI und ihre Bedeutung zu detektieren, bedarf es in Zukunft weiterer klinischer und experimenteller Arbeiten.

4.2. Publikation 2: Screening for severe drug-drug interactions in patients with multiple sclerosis: a comparison of three drug interaction databases

Die Therapie von PwMS basiert auf der Behandlung der grundlegenden Erkrankung, assoziierter MS-Symptome und weiterer Komorbiditäten. Durch die komplexe Therapiestrategie ergibt sich ein hohes Risiko für pDDI, die mithilfe von DDID identifiziert werden können. In der vorliegenden Arbeit wurden soziodemographische und klinische Prädiktoren, die das Auftreten von schweren pDDI begünstigen, ermittelt. Außerdem lag ein Vergleich der drei DDID (*Drugs.com*, *MediQ* und *Stockley´s*) im Zentrum dieser Arbeit. Die DDID wurden hinsichtlich der Identifikationsrate und Schweregradklassifizierung von pDDI in der Patientenkohorte verglichen.

Aus den Risikofaktoren für schwere pDDI stellte sich ein hoher Bildungsgrad als protektive Variable dar. In einer Studie von Hughes *et al.* konnte an 1466 Personen im Alter von über 70 Jahren nachgewiesen werden, dass Patienten mit einem höheren Bildungsgrad seltener schwere kardiovaskuläre und zentralnervöse pDDI aufwiesen [87]. Eine mögliche Begründung für den protektiven Effekt eines hohen Bildungsgrades liegt in der Gesundheitskompetenz. Dies meint die Fähigkeit, medizinische Informationen zu verstehen und zu bewerten, sodass Entscheidungen und Maßnahmen getroffen werden können, die dem Gesundheitszustand förderlich sind [88]. Für Patienten mit einem hohem Bildungsniveau (Hochschulabschluss) ist das Maß an Gesundheitskompetenz höher im Vergleich zu einem geringeren Bildungsgrad (Sekundarstufe II) [89]. Eine geringe Gesundheitskompetenz kann vor allem bei chronischen Erkrankungen die Erzielung optimaler Therapieergebnisse behindern [90].

Als prädiktive Faktoren, die das Auftreten schwerwiegender pDDI begünstigen, wurden ein höheres Patientenalter, eine zunehmende Anzahl von Medikamenten, das Vorhandensein von Komorbiditäten und ein geringeres Bildungsniveau identifiziert. Frühere Studien beschrieben bereits einen Zusammenhang von Polypharmazie mit höherem Alter, Komorbiditäten, höherem EDSS-Score, hoher Medikamentenanzahl, stationärer Behandlung sowie höherer Anzahl verschreibender Ärzte und ein damit einhergehendes erhöhtes Risiko für pDDI [35, 37, 62, 91–93]. In einer Studie mit 181 Demenzpatienten im stationären geriatrischen Setting waren vermehrte Medikamenteneinnahmen, Depressionen, der Schweregrad der Demenz und die Belastung des Pflegepersonals maßgeblich mit dem Auftreten schwerer pDDI assoziiert [57]. Da PwMS aufgrund von variierenden Symptomausprägungen (z. B. Spastik oder vegetative Dysfunktion) und begleitenden Komorbiditäten (z. B. kardiovaskuläre Erkrankungen) Medikamentenverschreibungen

verschiedener Fachdisziplinen erhalten, kann es passieren, dass es keinen beaufsichtigenden Arzt gibt, der den Überblick behält und die Gefahr für pDDI entdecken kann. Eine dänische Registerstudie konnte nachweisen, dass ein Drittel der PmP, die Medikamentenverschreibungen von fünf oder mehr Ärzten erhielten, ein deutlich erhöhtes Risiko für das Auftreten von pDDI hatten [92]. In Zukunft könnten elektronische Patientenakten das pDDI-Risiko durch den unkomplizierten Zugang zur Diagnose- und Medikamentenliste für alle behandelnden Ärzte und Apotheker verringern.

Insgesamt wurden in den drei DDID 1684 pDDI (gezählt ohne Wiederholung) identifiziert, wovon nur 318 pDDI (18,9%) von allen drei DDID gemeinsam detektiert wurden. Die höchste Anzahl unterschiedlicher pDDI wurde von *MediQ* (1161 pDDI) identifiziert, wobei es sich dabei überwiegend um leichte pDDI (82,5%) handelte. Weniger als 1% wurden von *MediQ* als schwerwiegende pDDI eingestuft. Mittels *Stockley´s* wurde insgesamt die geringste Anzahl von pDDI (706 pDDI) detektiert, jedoch mit dem höchsten Anteil schwerwiegender pDDI (37,4%). *Drugs.com* wurde mit 923 pDDI und davon 14,4% schweren pDDI im Mittelfeld verordnet. Der größte Übereinstimmungsanteil detektierter pDDI existierte zwischen *MediQ* und *Drugs.com* (37,0%) und die geringste Übereinstimmung zwischen *MediQ* und *Stockley´s* (31,1%). Im Hinblick auf die Schweregradeinordnung fand sich der größte Überlappungsgrad zwischen *Drugs.com* und *Stockley´s* (60,0%). Insgesamt wurden nur 3,3% der identifizierten pDDI mit dem gleichen Schweregrad in allen DDID beurteilt. Sechs pDDI waren in allen drei DDID als schwer eingestuft, wobei Citalopram an jeder dieser pDDI beteiligt war. Für einige DMD, wie Cladribin oder Natalizumab, konnten schwere pDDI nachgewiesen werden. Durchschnittlich gab es sechs pDDI (5,7±9,4) jeglichen Schweregrades bzw. eine schwere pDDI (0,9±2,0) pro PwMS in mindestens einer DDID. Bei 221 (35,2%) Patienten wurde eine oder mehrere schwere pDDI in mindestens einer DDID detektiert.

In der vorliegenden Arbeit war Citalopram an jeder schweren pDDI beteiligt, die übereinstimmend durch alle drei DDID detektiert wurde und insgesamt an 33 schweren pDDI nach mindestens einer DDID. Als selektiver Serotonin-Wiederaufnahmehemmer wird Citalopram bei PwMS mit Depressionen oder Angstzuständen verschrieben. Als negative Folge dieser pDDI kann es zu Herzrhythmusstörungen kommen [81]. Eine häufige Beteiligung von Citalopram an schweren pDDI konnte bereits in einer Studie demenzerkrankter Patienten gezeigt werden. Hier war Citalopram an der Hälfte der zehn häufigsten schweren pDDI beteiligt [57].

4.3. Publikation 3: Therapy of women with multiple sclerosis: an analysis of the use of drugs that may have adverse effects on the unborn child in the event of (unplanned) pregnancy

In der deutschen Allgemeinbevölkerung sind knapp 30% der Schwangerschaften unbeabsichtigt [27]. Im Rahmen einer medikamentenexponierten Schwangerschaft kann es zu pränatalen Schädigungen kommen. Bei Patientinnen mit MS gibt es daher eine Empfehlung zur sicheren Empfängnisverhütung unter DMD-Therapie [94]. Dies macht ein adäquates Medikamentenmanagement, insbesondere bei Frauen im gebärfähigen Alter, essentiell. Limitierte Daten zur Arzneimitteltherapiesicherheit vor und während einer Schwangerschaft stellen für das Therapiemanagement bei PwMS eine Herausforderung dar. In dieser Arbeit wurde das Risikopotenzial von Medikamenten für pränatale Schädigungen bei Frauen mit MS im gebärfähigen Alter zwischen 18 und 48 Jahren mithilfe von vier Datenbanken analysiert. Zu den MS-Patientinnen wurden soziodemographische, klinische und pharmazeutische Daten erhoben. Die eingenommenen Medikamente wurden mit vier evidenzbasierten Datenbanken (*Embryotox*, *Reprotox*, *TGA*, *SmPC*) auf das Gefährdungspotenzial für die pränatale Entwicklung untersucht. Je nach Schädigungspotenzial erfolgte die Einteilung in drei Kategorien (kein Effekt bis mögliche Wechselwirkungen auf das Ungeborene).

Eine Unterteilung der 212 Frauen mit MS erfolgte in 101 (47,6%) Patientinnen mit Kontrazeptiva-Gebrauch (PmCo) und 111 (52,4%) Patientinnen ohne Kontrazeptiva-Gebrauch (PoCo). Die Polypharmazierate bei Frauen im gebärfähigen Alter mit MS lag bei 39,2%. Für PmCo konnte ermittelt werden, dass sie dreimal häufiger Polypharmazie (59,4% vs. 20,7%), einen höheren Behinderungsgrad (EDSS-Score +0,5 Punkte) sowie eine höhere Anzahl an Komorbiditäten (+14,2%) im Vergleich zu PoCo hatten. Insgesamt wurden von den untersuchten MS-Patientinnen 182 verschiedene Medikamente eingenommen. Die vier verwendeten Datenbanken hatten ein heterogenes Bewertungsmuster hinsichtlich der Risikoeinschätzung u. a. aufgrund verschiedenen hinterlegten Informationen. Während *Embryotox* nur acht Medikamente als potenziell schädigend deklarierte, zeigte *SmPC* 149 Medikamente mit potenziell schädlichen Effekten an. Fast 94% der Patientinnen nahmen eine oder mehr Substanzen ein, die laut mindestens einer Datenbank mit einem potenziell schädigenden Effekt auf den Fetus einhergeht. Es nahmen 7,5% der Patientinnen mindestens ein Medikament ein, welches nach allen vier Datenbanken ein pränatales Risiko birgt. Bemerkenswert ist, dass 99 PoCo (89,2%) ein oder mehrere während einer Schwangerschaft nicht empfohlene Medikamente laut mindestens einer Datenbank verwendeten. Die am

häufigsten verwendeten DMD waren IFN-β-1a und GA, die von einem Viertel der Patientinnen eingenommen wurden (53 Patientinnen, 25,0%). Mit IFN-β-1a, Fingolimod, Ibuprofen und Pantoprazol wurden vier der acht am häufigsten verwendeten Wirkstoffe in mindestens zwei Datenbanken als potentiell gefährlich eingestuft.

In dieser Arbeit konnten 101 Patientinnen, die eine hormonelle Kontrazeption anwendeten, identifiziert werden. Im Vergleich mit einer Studie zu Verhütungsmethoden in Deutschland verwenden weniger MS-Patientinnen eine orale Kontrazeption, als die Allgemeinbevölkerung (47,6% vs. 62,1%) [95]. Aufgrund der von DMD und Non-DMD-Arzneimitteln ausgehenden Gefahr für eine gestörte pränatale Entwicklung bei einer eintretenden Schwangerschaft ist eine sichere Verhütungsmethode bei Patientinnen mit MS empfohlen [18]. Leitlinien wie die *US Medical Eligibility Criteria for Contraceptive Use* empfehlen jedoch bei Patientinnen mit längerer Immobilität aufgrund des höheren Risikos für venöse Thromboembolien in erster Linie die Verwendung von kupferhaltigen oder Levonorgestrel-freisetzenden Intrauterinpessaren [94].

Zum ersten Mal wurde eine umfassende Analyse einer Patientenkohorte mit MS im gebärfähigen Alter auf potenziell pränatal schädliche Medikamente, inklusive DMD und Non-DMD, durchgeführt. In der Literatur gibt es bislang nur Studien, die den Einfluss ausgewählter Medikamente (z. B. Ondansetron) auf die pränatale Entwicklung mithilfe einer Datenbank (z. B. Reprotox) untersuchten [96, 97]. Auch in Bezug auf die Anwendung mehrerer Datenbanken führt diese Publikation erstmals eine vergleichende Studie mit vier evidenzbasierten Datenbanken auf deren Identifikationsrate und Schweregradzuordnung von Medikamenten mit potenziell pränatal toxischen Einfluss durch.

Hinsichtlich der spezifischen MS-Therapie zählten IFN-β-1a und GA zu den meistverwendeten DMD in dieser Arbeit. Dies steht im Einklang mit nationalen und internationalen Empfehlungen, welche eine Therapie mit IFN-β-1a und GA bis zum Eintritt der Schwangerschaft und bei schwerer Krankheitsaktivität der MS auch während der Schwangerschaft empfehlen [13, 18, 23]. Die Wahl der MS-Therapie sollte bei der Familienplanung berücksichtigt werden und eine rechtzeitige Beratung über Therapiemöglichkeiten bei eintretender Schwangerschaft erfolgen [13]. Für die Patientin stellt dies eine komplexe Entscheidungssituation zwischen einem erhöhtem Schubrisiko bei Pausierung der DMD oder der Gefahr potenziell pränataler Schädigungen bei Fortführung der DMD-Therapie im Rahmen einer Schwangerschaft dar [98].

5. Integrative Betrachtung

Besonders bei PwMS kommt es durch ein komplexes Medikationsspektrum häufig zur Einnahme einer Vielzahl von Arzneimitteln, NEM und CAM. Wie in Publikation [1] beschrieben, stellt Polypharmazie einen Risikofaktor für ein vermehrtes Auftreten von pDDI dar [62]. Zur Identifikation von pDDI gibt es verschiedene DDID, deren Identifikationsrate und Schweregradklassifikation in Publikation [2] vergleichend dargestellt wurden [63]. Ein sicheres Therapiemanagement ist ausdrücklich bei Schwangeren oder Frauen mit Kinderwunsch essentiell, um potenziell pränatalen Schädigungen vorzubeugen. Publikation [3] zeigt die Prävalenz von potenziell pränatal toxischen Medikamenten bei MS-Patientinnen im gebärfähigen Alter [64].

Die Gesamtstudienpopulation (n=627) ist aus soziodemographischen und klinisch-neurologischen Gesichtspunkten repräsentativ, wenn man große nationale MS-Studien als Referenzen heranzieht [14, 123]. In der Patientenkohorte konnte eine Polypharmazierate von 53,3% gefunden werden. PmP wiesen außerdem zehnmal häufiger schwere pDDI auf, als PoP (17,7% vs. 1,7%). Die dargestellte Polypharmazierate steht mit den Ergebnissen anderer Studien im Einklang [31, 34]. Die identifizierten pDDI-Raten stellen neue Erkenntnisse dar, weil es bislang keine Studien anderer Arbeitsgruppen zu pDDI bei PwMS gibt. Bei PmP besteht einerseits die Gefahr, dass medikamenten-bedingte UAW fälschlicherweise als neue Symptome einer Erkrankung gedeutet werden und daraus Verschreibungskaskaden folgen können [32, 99]. Andererseits kann der Behandler bei bekannter Polypharmazie dazu geneigt sein, trotz gerechtfertigter Indikation, keine weiteren Medikamente zu verschreiben. Eine Untersuchung zeigte, dass mit zunehmender Anzahl von Medikamenten die Wahrscheinlichkeit einer Unterbehandlung steigt [100]. Für ein adäquates Therapiemanagement sollte eine regelmäßige Prüfung des Medikationsplan auf Notwendigkeit der Therapie erfolgen und bei neuaufgetretenen Symptomen potenzielle UAW in Betracht gezogen werden. Für die Behandlung von älteren PmP existieren verschiedene Listen, um die Pharmakotherapie anzupassen. Beispielsweise gibt die FORTA-Liste Empfehlungen zu geeigneten und ungeeigneten Medikamenten bei geriatrischen Patienten [32]. Für die Betreuung von Schwangeren gibt es Datenbanken wie *Embryotox*, die Empfehlungen für eine sichere Arzneimitteltherapie in der Schwangerschaft geben. Die KIDs-Liste (*Key Potentially Inappropriate Drugs in Pediatrics*) empfiehlt sichere Arzneimittel für pädiatrische Patienten [101]. Für chronisch erkrankte PmP im mittleren Erwachsenenalter gibt es bislang keine vergleichbaren Listen, um die Pharmakotherapie sicherer und effektiver zu gestalten.

Hinsichtlich der Detektionsrate von pDDI lag die gemeinsame Schnittmenge der drei DDID (*Drugs.com*, *MediQ* und *Stockley´s*) in der vorliegenden Arbeit bei 18,9%. Nur sechs pDDI wurden konsistent als schwer eingestuft. Insgesamt waren die Übereinstimmungsgrade zwischen jeweils zwei DDID gering (31,1% bis 37,0%, Publikation 2). Die festgestellten Abweichungen der DDID lassen sich im Vergleich mit ähnlichen Studien bestätigen. Die Übereinstimmungsgrade der detektierten pDDI durch alle angewandten DDID innerhalb der externen Studien lagen in einem Bereich zwischen 5% und 44% [49–55]. Damit liegt der in Publikation 2 ermittelte Wert innerhalb der Spannweite und kann die bisherigen Ergebnisse anderer Arbeits- und Forschungsgruppen bekräftigen. Eine Begründung für den geringen Überlappungsgrad der DDID kann in der stark variierenden Anzahl hinterlegter Wirkstoffe und pDDI liegen. Beispielsweise sind in *Stockley´s* über mehr als 110.000 pDDI hinterlegt, während in *MediQ* auf weniger als die Hälfte an pDDI (über 52.000 pDDI) zurückgegriffen wird. Trotzdem konnte in der vorliegenden Arbeit beobachtet werden, dass die meisten pDDI von *MediQ* (1161 pDDI) und die geringste pDDI-Anzahl von *Stockley´s* (706 pDDI) angegeben wurde. Einerseits gibt es bisher keine standardisierte Definition und damit verbindliche Rechtlinie, ab wann es sich um eine pDDI handelt [102]. Ob ein Medikamentenpaar interagiert, hängt von multiplen Faktoren ab (z. B. Einnahmeintervall, Verabreichungsform), die in den DDID in unterschiedlichen Ausmaß berücksichtigt werden. Andererseits, wie bereits in Publikation 2 [63]und anderen Arbeitsgruppen beschrieben [55, 56], sind einige Wirkstoffe in den Datenbanken nicht aufzufinden, wie Propiverin oder Metamizol (eingeschränkte Zulassung [103]) bei *Drugs.com*. Daher sollte im klinischen Alltag mehr als eine DDID verwendet oder ein klinischer Pharmazeut hinzugezogen werden, solange es keine besseren Lösungen gibt [54, 56, 104].

Im Hinblick auf die pDDI-Schweregradzuordnung wurden in der vorliegenden Arbeit nur 3,3% der pDDI mit dem gleichen Schweregrad von den verwendeten DDID beurteilt (Publikation 2) [63]. Die größte Deckungsgleichheit bezüglich der Schweregradzuordnung zeigte sich zwischen *Drugs.com* und *Stockley´s* (60,0%). Während durch MediQ weniger als 1% der pDDI als schwer klassifiziert wurde, ergab sich bei Drugs.com ein Anteil schwerer pDDI von 14,4% und bei Stockley´s von 37,4%. In einer Studie unter Verwendung von *Micromedex* und *Drugs.com* wurden bei ebenfalls 37,4% der pDDI kongruente Schweregrade festgestellt [105]. Prely *et al*. fanden unter Verwendung von *Thériaque* und *Drugs.com*, dass nur 2,5% der pDDI mit dem gleichen Schweregrad bewertet wurden [40]. Ob für ein Medikamentenpaar eine pDDI in verschiedenen DDID übereinstimmend mit dem gleichen Schweregrad angegeben ist, hängt wesentlich von der Aktualität der Datenbanken und der Anzahl hinterlegter Wirkstoffe und pDDI in den einzelnen DDID ab. Nach sämtlichen

Aktualisierungen von sechs DDID nach einem Zeitraum von zwei Jahren konnte ein Anstieg der prozentualen Übereinstimmungsrate für pDDI von nur 1% festgestellt werden [104]. Außerdem konnte gezeigt werden, dass es unter den DDID uneinheitliche Bewertungssysteme für die Schweregrade gibt [35, 62, 63, 102]. Die große Spannweite identifizierter schwerer pDDI in dieser Arbeit kann zum einen in der Zielgruppe der DDID begründet sein. *Drugs.com* ist in erster Linie eine patientenzentrierte DDID, während es sich bei *Stockley´s* und *MediQ* um DDID für die täglich klinische Anwendung durch medinische Fachexperten handelt. Für Patienten sind schwere pDDI bedeutsamer, um vorsichtshalber einen Arzt aufzusuchen zu können. Eine große Informationsmenge zu milden und mäßigen pDDI kann bei den Patienten zur Verwirrung führen [105]. Zum anderen sollen schwere pDDI-Warnungen frühzeitig auf UAW aufmerksam machen. Allerdings besteht die Gefahr, dass der Anwender bei der Anzeige vieler schwerwiegender pDDI dazu neigt, sie als weniger gravierend einzustufen und zu übersehen, im Vergleich zur Darstellung einzelner schwerwiegender pDDI [106].

Die Prävalenz von pDDI in der MS-Kohorte lag bei 65,1% (Publikation 1) [62]. Bislang existieren keine anderen Studien außerhalb unserer Arbeitsgruppe zu pDDI bei PwMS. Daher müssen Studien mit anderer Indikation herangezogen werden. In einer italienischen Populationsstudie wurde bei 45,3% der Allgemeinbevölkerung mindestens eine pDDI gefunden [107]. Bei onkologischen Patienten unter laufender Chemotherapie konnte ein pDDI-Prävalenz von 78% nachgewiesen werden [108]. Zur Einschätzung der Relevanz von pDDI ist es wichtig zu beachten, dass nur ein geringer Prozentsatz tatsächlich klinisch in Form von UAW, veränderten Wirkstoffspiegeln im Blut oder unzureichender Therapiewirkung zu tragen kommt [109, 110]. Ein systematisches Review fand klinisch relevante pDDI in weniger als 1 von 10 Patienten (gepoolte pDDI-Prävalenz: 9,2%) [109]. In einer prospektiven Kohortenstudie bei Patienten mit Organtransplantationen unter immunsuppressiver Therapie (n=309) konnte mittels DDID bei jedem Patienten eine moderate oder höhergradige pDDI nachgewiesen werden, wobei die reale pDDI-Prävalenz bei 21,7% lag. Der Großteil der klinisch signifikanten pDDI basierte auf Veränderungen des Wirkstoffspiegels im Blut bei asymptomatischen Patienten. Bei nur 22 Patienten (7,1%) waren UAW aufgetreten [110]. Oftmals werden daher pDDI nach vorheriger Abwägung bewusst toleriert [111], weshalb die hohe pDDI-Prävalenz in dieser Arbeit zu relativieren ist. Mehrere Studien erbrachten den Nachweis, dass ausgegebene pDDI-Warnungen übergangen wurden, weil sie durch den Anwender als unangemessen bewertet wurden, wenn beispielsweise bereits Dosisanpassungen erfolgten oder Laboruntersuchungen angeordnet wurden [104, 106, 111]. Einige Ansätze für eine präzisere Vorhersage von klinisch relevanten pDDI beschreiben

Hammar *et al*. sowie Wasylewicz *et al* in ihren Arbeiten [105, 112]. Beim kontextbezogenen pDDI-Management werden verschiedene Patientenparameter, Medikamentendosierungen und Laborwerte in die reguläre DDID integriert, worunter eine erhebliche Senkung der Anzahl irrelevanter pDDI-Warnungen erzielt werden konnte [112].

Bei Frauen im gebärfähigen Alter mit MS lag die Prävalenz von Polypharmazie bei 39,2%. Für 93,4% der Frauen konnte nachgewiesen werden, dass sie mindestens ein Medikament einnahmen, das laut mindestens einer Datenbank einen potenziell pränatal schädlichen Effekt hat. Unter Berücksichtigung aller vier angewandten Datenbanken fand sich bei 7,5% der Patientinnen für mindestens ein Medikament eine gemeinsame Einstufung als potenziell pränatal toxisch (Publikation 3) [64]. Erstmals konnte eine Polypharmazierate bei Frauen im gebärfähigen Alter mit MS beschrieben werden, da bislang keine Studien anderer Arbeitsgruppen vorliegen. In einer unselektiven Longitudinalstudie von 9546 erstgebärenden Frauen im ersten Trimester, die ein oder mehrere Medikamente nahmen, lag die Polypharmazierate bei 30,5% [113]. Somit hat das Therapieregime bei MS einen nicht unerheblichen Einfluss auf das Vorkommen von Polypharmazie bei jungen an MS-erkrankten Frauen. Zur Analyse potenziell pränatal schädlicher Medikamente durch eine oder mehrere Datenbanken gibt es bislang keine vergleichbaren Studien weder bei MS, noch generell bei Schwangeren bzw. Frauen im gebärfähigen Alter. Wir konnten zeigen, dass die vier verwendeten Datenbanken ein heterogenes Bewertungsmuster hinsichtlich Identifikationsrate und Zuordnung des pränatalen Schädigungspotenzials aufweisen. Die Gründe für den geringen Übereinstimmungsgrad der vier Datenbanken sind multifaktoriell [63]. Jede Datenbank hat eine eigene Risikoklassifizierung und einen uneinheitlichen Definitionsbereich, ab wann ein Medikament als potenziell pränatal toxisch gewertet wird. Daher erfolgte in dieser Arbeit die Zuweisung der einzelnen Schweregrade der Datenbanken in drei Kategorien (kein Effekt bis mögliche Wechselwirkungen auf den Fetus). Außerdem ist das Wissen zur Medikamentensicherheit in der Schwangerschaft begrenzt, da randomisierte kontrollierte Studien schwangere Frauen in der Regel ausschließen und sich in erster Linie auf die Therapiewirksamkeit, anstelle potenziell pränatal schädlicher Effekte konzentrieren [114, 115]. Die Untersuchung der Arzneimittelsicherheit in der Schwangerschaft basiert neben tierexperimentellen Studien v. a. auf Beobachtungsstudien in Form prospektiver Kohortenstudien und retrospektiven Fall-Kontroll-Studien [114, 115]. Des Weiteren sind einige Wirkstoffe in den Datenbanken nicht auffindbar (z. B. DMD, wie Ocrelizumab oder Cladribin bei *Embryotox*). Dies birgt das Risiko potenziell pränatal toxische UAW im Therapiemanagement nicht zu berücksichtigen. Die Warnungen zu potenziell frühkindlich schädigenden Medikamenten sollten beachtet und individuell abgewogen werden. Es sollten

Arzneimittel verwendet werden, für die Erfahrungen bei der Anwendung in der Schwangerschaft vorliegen und bei denen keine pränatal schädlichen UAW vermutet werden [116].

In dieser Arbeit konnte das Auftreten von Polypharmazie bei 334 PwMS (53,3%) nachgewiesen werden. Für PmP zeigte sich ein rund 17-fach erhöhtes Risiko für das Auftreten von schweren pDDI, sodass ein adäquates medikamentöses Management essentiell zur Vermeidung negativer gesundheitlicher Folgen ist. Um einen unangemessenen Arzneimittelgebrauch zu vermeiden, sollte der Medikationsplan bei jedem Patientenkontakt auf gültige Indikation, mögliche Interaktionspartner und den berichteten Nutzen des Patienten überprüft werden [77]. Wenn das Medikament dem Patienten keinen nachweisbaren Vorteil erbringt, UAW auftreten oder vom Patienten gesetzte Therapieziele nicht erfüllt werden, sollte über ein Absetzen des Medikamentes diskutiert werden (z. B. Antispastika bei MS) [77]. Unter dem Begriff „Deprescribing“ wird das Verringern oder Absetzen von Medikamenten zusammengefasst [117]. Außerdem sollten Ärzte die Patienten über das richtige Einnahmeverhalten (z. B. Einnahmeintervall) aufklären, sicherstellen, dass die Instruktionen verstanden wurden, und die richtige Anwendung durch Nachfrage überprüfen. Für eine rechtzeitige ärztliche Konsultation im Notfall, ist es sinnvoll, dass der Patient über erste Anzeichen von UAW aufgeklärt ist.

Im folgenden Absatz soll auf Limitationen dieser Arbeit eingegangen werden. Es soll darauf hingewiesen werden, dass das tatsächliche Auftreten von pDDI in dieser Arbeit nicht erfasst wurde, sondern es sich bei den identifizierten pDDI oftmals um theoretische Konstrukte handelt. Die dargestellten pDDI müssen klinisch nicht zwingend auftreten, können jedoch mit einer erhöhten Auftretenswahrscheinlichkeit von UAW einhergehen. Die Therapieadhärenz, der genaue Zeitpunkt der Medikamenteneinnahme (z. B. Methylprednisolon), Stoffwechseleigenschaften (z. B. CYP-Metabolismus) oder UAW der Patienten wurden in der vorliegenden Arbeit u. a. nicht berücksichtigt. Bedingt durch das Querschnittsdesign der Studie haben wir keine Veränderungen der Medikationspläne im Verlauf durchgeführt. Zukünftige Studien könnten im longitudinalen Studiendesign die tatsächliche Relevanz ausgewählter pDDI anhand von UAW und Messungen von Medikamentenspiegeln (z. B. therapeutisches Drug-Monitoring) im Real-World-Setting bestimmen. Damit könnte die tatsächliche Relevanz von pDDI in der MS-Therapie besser abgeschätzt werden. Des Weiteren wurde das Wissen der behandelnden Ärzte zu pDDI nicht erfragt und ob pDDI als klinisch nicht signifikant eingeschätzt und daher akzeptiert wurden. Weitere Studien könnten Patienten untersuchen, ob sie sich über das Problem von pDDI bewusst sind und

Informationen zu pDDI verstehen. Zu den identifizierten pDFI in Publikation 1 soll erwähnt werden, dass im Rahmen dieser Studie keine Ernährungsgewohnheiten, der Zeitpunkt der Nahrungsmittelaufnahme sowie das Rauch-, Drogen- oder Alkoholverhalten der Patienten erfragt wurde. Zukünftige Studien könnten diese Parameter erheben, um die Wahrscheinlichkeit für das tatsächliche Auftreten von pDFI besser abzubilden.

In unserer Subpopulation der Frauen im gebärfähigen Alter wurden einige Kontrazeptionsmethoden (z. B. mechanische Verhütungsverfahren) nicht erfasst. Ebenfalls wurde der Schwangerschaftswunsch der 212 Frauen in der Auswertung nicht berücksichtigt. Wir haben keine Daten zu tatsächlich eingetretenen Schwangerschaften oder reale Auswirkungen von potenziell pränatal toxischen Medikamenten auf das Ungeborene erhoben. Nachfolgende Studien könnten sich mit dem Auftreten von medikamentenassoziierten Risiken für die männliche Fertilität beschäftigen.

Für den Erhalt möglichst vollständiger Daten wurde bei den Patienten eine Anamnese, eine klinische Untersuchung und ein Interview durchgeführt sowie die Patientenakten durchgesehen. Jedoch kann nicht ausgeschlossen werden, dass einzelne Präparate nicht erfasst wurden, da besonders im Bereich der rezeptfreien und pflanzlichen Präparate Patienten teilweise ungenaue oder keine Angaben machten. Einheitliche digitale Patientenakten wären ein sinnvolles Mittel, um unvollständigen Medikamentenangaben entgegenzuwirken und den verschreibenden Ärzten unterschiedlicher Fachbereiche einen aktuellen Medikamentenplan zu liefern. Es soll darauf hingewiesen werden, dass die in den drei Publikationen beschriebene Kohorte aus einer Datensammlung stammt und auf einem übergeordneten Gesamtkollektiv basiert. In die vorliegende Studie wurden zwei deutsche Zentren einbezogen, sodass generalisierte Aussagen für die MS-Therapie in Deutschland abgeleitet werden können. Es sollte jedoch beachtet werden, dass es international teilweise verschiedene Behandlungsstrategien und Verfügbarkeiten von Medikamenten gibt. Diese Arbeit konnte erstmals ein detailliertes Abbild über das derzeitige Risikopotenzial von pDDI und assoziierter Faktoren bei PwMS sowie die Prävalenz von Medikamenten mit potenziell schädlichen Einfluss auf die pränatale Entwicklung bei Frauen im gebärfähigen Alter im Real-World-Setting darstellen.

Bei Frauen im gebärfähigen Alter sollten regelmäßig ärztliche Konsultationen zur Evaluation der aktuellen Medikation, symptomatischer UAW und des Kinderwunsches erfolgen. Ein frühzeitig bekannter Kinderwunsch verschafft den behandelnden Ärzten ausreichend Zeit, um einen Medikationsplan entsprechend der mütterlichen und pränatalen Bedürfnisse zu erarbeiten. Dafür ist eine enge interdisziplinäre Kommunikation der behandelnden Ärzte wie

Neurologen, Gynäkologen, Pharmakologen oder Allgemeinmedizinern sinnvoll. Bei nicht angestrebter Familienplanung sollte die Notwendigkeit der Kontrazeption mit der Patientin wiederholend diskutiert werden, um ungewollte Schwangerschaften und ein mögliches Risiko für pränatal schädliche Arzneimittelwirkungen zu verhindern.

In Zukunft wäre ein Softwaretool für die klinische Praxis sinnvoll, welches bei Konsultation jedes Patienten den digitalen Medikationsplan automatisch im Hintergrund mittels eines Algorithmus auf pDDI analysiert. Der Behandler soll durch das Programm auf mögliche UAW hingewiesen werden, die aus den pDDI abgeleitet werden können. Das Tool sollte dabei Zugriff auf mehrere unterschiedliche Datenbanken zur Arzneimittelsicherheit haben, den potenziellen Schweregrad der pDDI und UAW einschätzen und bekannte Patienteninformationen fortführend in die Analyse integrieren (etwa Symptome, Laborwerte, Allergien) [112]. Im Erfolgsfall ergibt sich eine Zeit- und Kostenersparnis, wenn diagnostische Maßnahmen, längere Hospitalisationen und Verschreibungskaskaden vermieden werden. Eine weitere Säule könnten alternative Vorschläge zur Arzneimitteltherapie, CAM oder zu nicht-medikamentösen Therapieansätzen sein. Perspektivisch kann künstliche Intelligenz (in Form von maschinellen Lernen oder Deep Learning-Prozessen) durch präzisere Vorhersage von pDDI dazu beitragen die Patientensicherheit zu erhöhen und die Therapiestrategie zu optimieren [118–120]. Damit kann ein weiterer Schritt auf dem Weg zu einer sicheren und individualisierten Pharmakotherapie unternommen werden.

6. Zusammenfassung

Die Multiple Sklerose (MS) stellt eine chronisch-inflammatorische Erkrankung des ZNS dar und betrifft überwiegend Frauen. Der Krankheitsbeginn liegt häufig im jungen Erwachsenenalter. Klinisch zeigt sich die MS als „Krankheitsbild mit tausend verschiedenen Gesichtern“, sodass im langjährigen Krankheitsverlauf die Behandlung unterschiedlicher Symptome (z. B. Spastiken, Paresen) notwendig wird. Zur Verringerung der Krankheitsaktivität und zur Linderung MS-bezogener Symptome wird eine komplexe Therapiestrategie angewandt. Diese beinhaltet eine spezifische immunmodifizierende Therapie sowie die Verwendung von Symptomtherapeutika und Medikamenten zur Behandlung von potenziellen Komorbiditäten. Als Folge der medikamentenintensiven Behandlung besteht bereits bei jungen Patienten ein hohes Risiko für Polypharmazie (gleichzeitige Einnahme von mindestens fünf Therapeutika). Durch die Einnahme zahlreicher Medikamente ist die Wahrscheinlichkeit von potenziellen Medikamenteninteraktionen (potential drug-drug interactions, pDDI) erhöht. Durch pDDI kann es zu unerwünschten Arzneimittelwirkungen (UAW), Verschreibungskaskaden, höheren Gesundheitskosten sowie zu geringerer Therapieadhärenz bis hin zu einer erhöhten Mortalität kommen.

In einer Studienpopulation von 627 Patienten mit MS (PwMS) wurde die Prävalenz und der Schweregrad von pDDI mithilfe von Interaktionsdatenbanken (drug-drug interaction databases, DDID) untersucht [62]. Zusätzlich erfolgte die Analyse auf patientenspezifische und klinische Risikofaktoren für pDDI [62, 63]. Die drei verwendeten DDID konnten hinsichtlich der Identifizierung und Klassifizierung von pDDI vergleichend analysiert werden [63]. In einer Subpopulation von 212 MS-Patientinnen im gebärfähigen Alter wurde die potenzielle Gefahr für pränatale Schädigungen unter Medikamentenexposition untersucht [64].

Erstmals konnte für PwMS das Ausmaß hinsichtlich der Häufigkeit und Schwere von pDDI abgeschätzt werden. Dabei hatten MS-Patienten mit Polypharmazie (PmP) (n=334) ein 15-fach erhöhtes Risiko für schwere pDDI im Vergleich zu Patienten ohne Polypharmazie (PoP) [62]. Für 65,1% der PwMS konnte mindestens eine pDDI gefunden werden [62]. Als Prädiktoren für das Auftreten von schweren pDDI konnten ein höheres Alter, eine größere Anzahl eingenommener Präparate, vorhandene Komorbiditäten und ein geringeres Bildungsniveau detektiert werden [63]. Die DDID wiesen starke Diskrepanzen hinsichtlich der Anzahl identifizierter pDDI und der Schweregradbewertung auf. Nur 3,3% der pDDI wurden von allen untersuchten Datenbanken mit dem gleichen Schweregrad bewertet [63]. Bei 93,4% der Patientinnen im gebärfähigen Alter wurde mindestens ein Medikament

identifiziert, welches einen potenziell pränatal schädigenden Effekt haben kann [64]. Patientinnen mit Kontrazeptiva-Gebrauch (PmCo) wiesen signifikant häufiger Polypharmazie, einen höheren Behinderungsgrad und mehr Komorbiditäten auf, als Patientinnen ohne Kontrazeptiva-Anwendung (PoCo) [64].

Die Darstellung der Prävalenz von pDDI bei PwMS sowie des Risiko potenziell pränatal toxischer Medikamente bei Frauen im gebärfähigen Alter machen die Ergebnisse dieser Studien für das klinische Umfeld relevant. Durch Beachtung der mit pDDI-assoziierten Parameter können pDDI in potenziell gefährdeten Patientengruppen frühzeitig erkannt werden. Die präsentierten Studienergebnisse sollen zu einer kritischen Anwendung von DDID anregen und das Bewusstsein für Medikamente mit potenziell schädigenden Effekt auf die Mutter und die pränatale Entwicklung schärfen.

Ausgehend von den vorliegenden Daten könnten zukünftig klinische Zusammenhänge von pDDI und UAW in einer Longitudinalstudie untersucht werden, um das Ausmaß von klinisch relevanten pDDI bei PwMS über die Zeit zu detektieren und Langzeittrends zu untersuchen. Dies kann klinisch durch regelmäßige Analysen von UAW-bedingten Symptomen oder pharmakologisch durch die Bestimmung von Medikamentenspiegeln im Langzeitverlauf erfolgen. Durch Anwendung von künstlicher Intelligenz können Studien in Zukunft präzisere Vorhersagen zu pDDI machen und Therapiepläne optimieren. Das Ziel ist dabei, eine maßgeschneiderte und sichere Pharmakotherapie für den einzelnen Patienten zu entwickeln.

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8. Publikationen

8.1. Publikation 1

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

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, ⩾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 (± 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 [+standard deviation (SD)] was 48.6 (±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.
[a]Fisher's exact test.
[b]Range.
[c]Mean value (standard deviation).
[d]Two-sample two-tailed *t* test.
[e]Chi-squared test.
[f]Median.
[g]Mann–Whitney *U* test.
[h]Average number of drugs taken per patient (standard deviation).

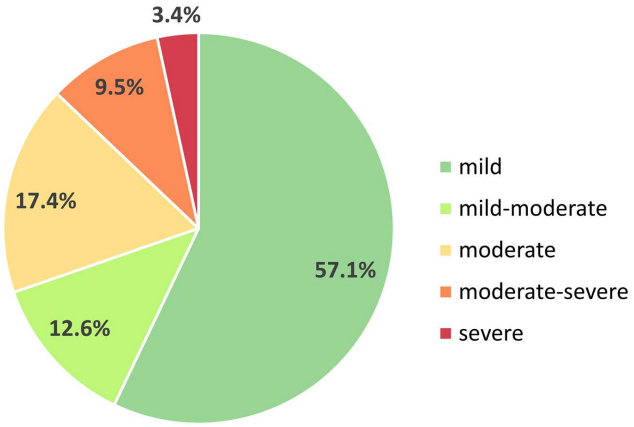

Figure 1. Percentage distribution of severity of drug–drug interactions in patients with MS. In this study, 627 MS patients had a total number of 2587 pDDIs. This chart shows the frequencies of the five pDDI severity levels. Most pDDIs were mild (57.1%), while moderate pDDIs had a share of 17.4%. Moderate-severe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

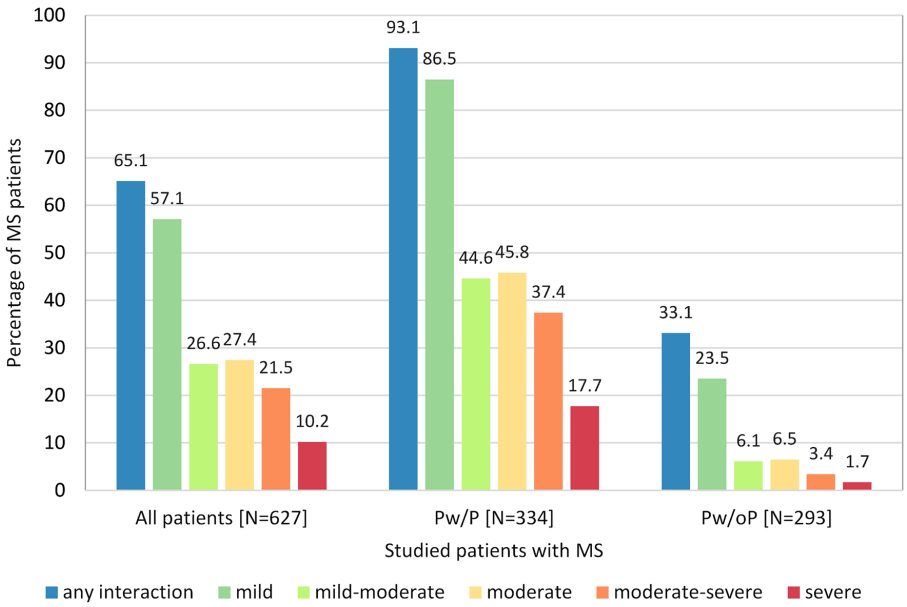

Figure 2. Comparison of the prevalence of pDDIs of different severity degrees between MS patients with and without polypharmacy. The proportion of patients having pDDIs was significantly higher in Pw/P *versus* Pw/oP for each degree of severity (Fisher's exact test $p < 0.001$). Pw/P were three times 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 ⇔ fingolimod ($N = 7$ patients) and acetylsalicylic acid ⇔ ibuprofen ($N = 6$ patients). The moderate-severe pDDIs acetylsalicylic acid ⇔ enoxaparin, ibuprofen ⇔ enoxaparin, methylprednisolone ⇔ ibuprofen, enoxaparin ⇔ ramipril and citalopram ⇔ 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 ⇔ 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 ⇔ 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	Mild-severe	Moderate	Moderate-severe	Severe	Total (*N* = 627)	Pw/P (*N* = 334)	Pw/oP (*N* = 293)	
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**
Torasemide	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/oP, patients without polypharmacy; Pw/P, patients with polypharmacy.

[a]*p*: *p*-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.
[a]*p: 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

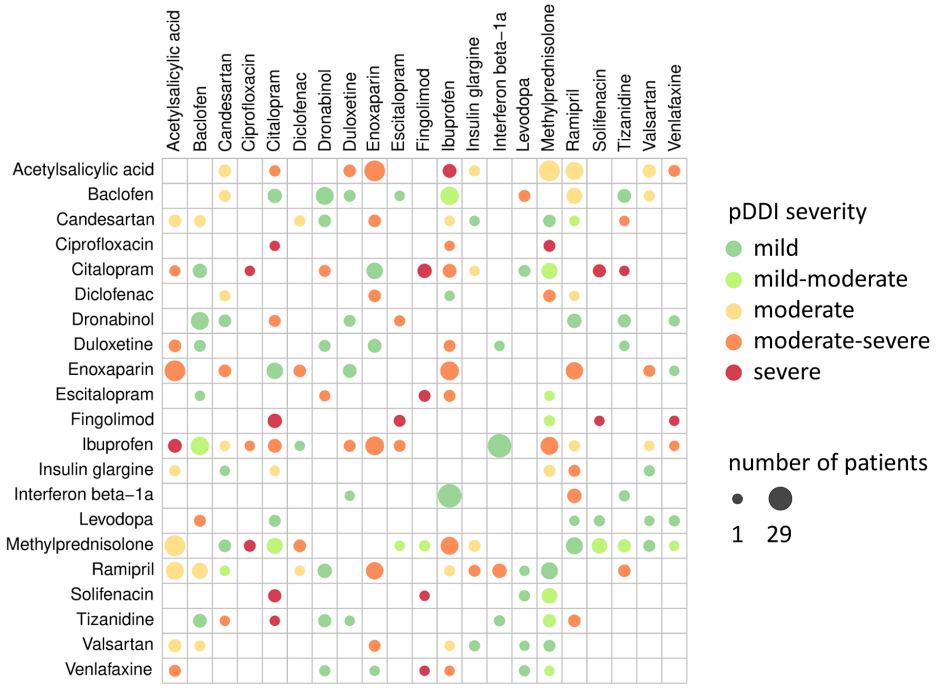

Figure 3. Interaction heatmap of drugs for which moderate-severe or severe pDDIs have been repeatedly noted in patients with MS. Shown is the frequency and severity of pDDIs between drugs involved in moderate-severe or severe pDDIs that were identified in at least three patients with MS (see also Table 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.
[a]Dietary fibre, milk, soy products, coffee, nuts and seeds.
[b]Foods 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

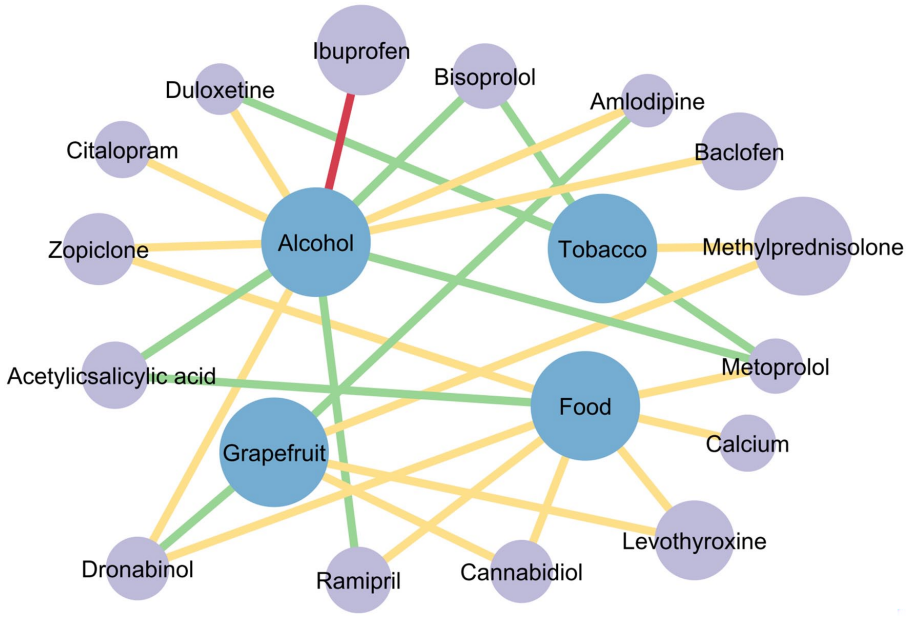

Figure 4. Network of pDFIs for the top 20 drugs for which the most pDDIs were recorded. Grey dots stand for medications and blue dots represent other substances. The size of the grey dots shows the number of patients taking this drug (e.g. methylprednisolone was taken by 123 patients). The line colour 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 ⇔ enoxaparin ($N = 21$ patients, 3.3%) and enoxaparin ⇔ 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 dead.[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 (=tetrahydrocannabidiol, 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 childbearing 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 ⇔ 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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Uwe Klaus Zettl: Conceptualisation; Methodology; Supervision; Writing – review & editing.

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Competing interests

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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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8.2. Publikation 2

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; Suriyapakorn 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 (Suriyapakorn 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 ± 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

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

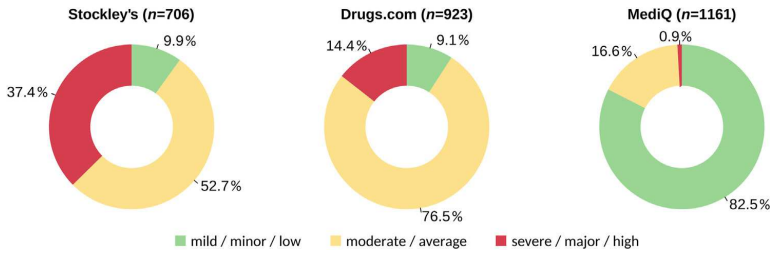

FIGURE 1
Proportions of mild, moderate and severe potential drug-drug interactions by database. The medication schedules of 627 patients with CIS/MS were evaluated with respect to pDDIs using three databases. The doughnut plots show the proportions across all different pDDIs found. CIS, clinically isolated syndrome; MS, multiple sclerosis; pDDI, potential drug-drug interaction.

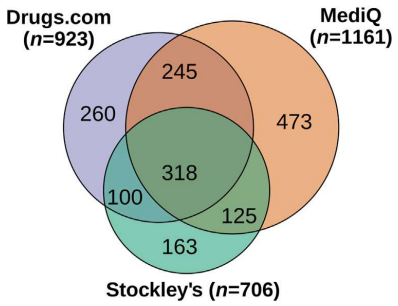

FIGURE 2
Overlap of potential drug-drug interactions among the three databases. A total of 1,684 different pDDIs were identified for the patient cohort (N = 627). The Venn diagram shows the intersections of pDDIs between the databases. The circles and intersecting sets are drawn approximately to scale. pDDI, potential drug-drug interaction.

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.,

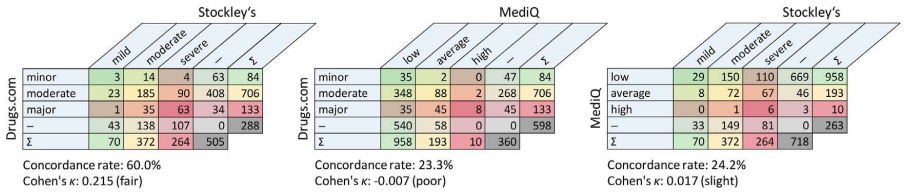

FIGURE 3
Pairwise comparisons of the databases in terms of reported potential drug-drug interactions by degree of severity. The crosstabs show the overlaps related to different pDDIs. The cells in the tables are color-coded according to pDDI severity from mild (green) to severe (red). — = not recorded in one of the two databases; ∑ = sum per row/column; pDDI, potential drug-drug interaction.

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%)
Dipyrone/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 aci < = > Dipyrone/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, *n* (%)	Severe pDDIs according to Drugs.com only	Frequency, *n* (%)
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%)
Dipyrone/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%)
Beclometasone < = > Escitalopram	1 (0.2%)	Diclofenac < = > Teriflunomide	1 (0.2%)
Betamethasone < = > Dipyrone/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%)
Bicalutamide < = > Goserelin	1 (0.2%)	Mirabegron < = > Tamoxifen	1 (0.2%)
Bicalutamide < = > 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.

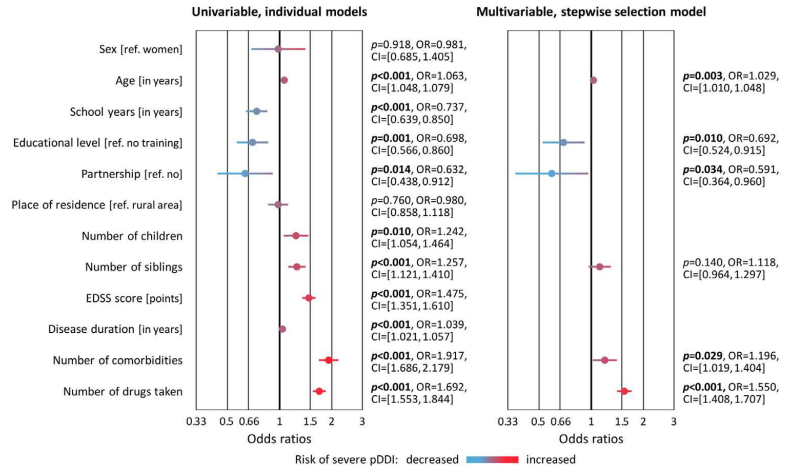

FIGURE 4
Factors associated with the occurrence of severe potential drug-drug interactions in patients with multiple sclerosis. A subset of 221 of the 627 patients had at least one severe pDDI according to at least one of the three databases used. Binary logistic regression analyses were performed to 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; Suriyapakorn 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 (Théroux 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

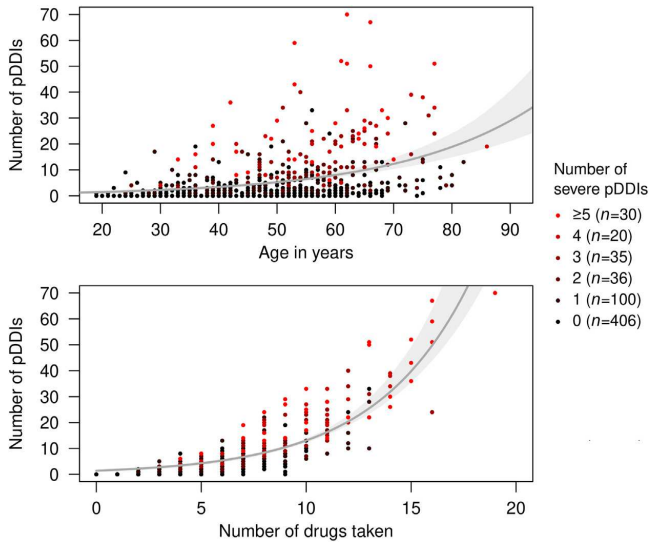

FIGURE 5
Frequency of potential drug-drug interactions in relation to age and number of drugs taken. The patients (N = 627) took 5.3 medications on average. A subset of 441 patients had at least one pDDI according to at least one of the three databases used. Red dots in the scatterplot represent patients with multiple severe pDDIs. Fitted exponential curves with 95% bootstrap confidence intervals are shown in gray. pDDI, potential drug-drug interaction.

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; Zanghì 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.

Publisher's note

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.

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8.3. Publikation 3

Therapy of women with multiple sclerosis: an analysis of the use of drugs that may have adverse effects on the unborn child in the event of (unplanned) pregnancy

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Therapy of women with multiple sclerosis: an analysis of the use of drugs that may have adverse effects on the unborn child in the event of (unplanned) pregnancy

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Abstract

Background: Although effective contraception is strongly recommended during the therapy of women with multiple sclerosis (MS) with some immunomodulatory drugs, unplanned pregnancies still occur. Adequate medication management is essential to avoid foetal harm in the event of an unplanned pregnancy.

Objective: The aim was to screen for medications used in women of childbearing age with MS that may pose a risk of side effects on foetal development.

Methods: Sociodemographic, clinical and medication data were collected from 212 women with MS by structured interviews, clinical examinations and medical records. Using the databases from Embryotox, Reprotox, the Therapeutic Goods Administration and on the German summaries of product characteristics, we assessed whether the taken drugs were potentially harmful regarding the foetal development.

Results: The majority of patients (93.4%) were taking one or more drugs for which a possible harmful effect on the foetus is indicated in at least one of the four databases used. This proportion was even higher in patients who used hormonal contraceptives (birth control pills or vaginal rings) (PwCo, $n = 101$), but it was also quite high in patients who did not use such contraceptives (Pw/oCo, $n = 111$) (98.0% and 89.2%, respectively). PwCo were significantly more likely to take five or more medications with potential foetal risk according to at least one database than Pw/oCo (31.7% *versus* 6.3%). PwCo were also more severely disabled (average Expanded Disability Status Scale score: 2.8 *versus* 2.3) and more frequently had comorbidities (68.3% *versus* 54.1%) than Pw/oCo.

Conclusion: Data on the most commonly used drugs in MS therapy were gathered to study the risk of possible drug effects on foetal development in female MS patients of childbearing age. We found that the majority of drugs used by patients with MS are rated as having a potential risk of interfering with normal foetal development. More effective contraception and special pregnancy information programmes regarding the therapy management during pregnancy should be implemented to reduce potential risks to mother and child.

Plain Language Summary

Use of drugs not recommended during pregnancy by women with multiple sclerosis

Introduction: Patients with multiple sclerosis (MS) often have to take different drugs simultaneously. During the therapy with some immunomodulatory drugs, effective contraception is strongly recommended. Nevertheless, unplanned pregnancies occur regularly in women with MS.

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Methods: Here, we investigated whether the 212 patients included in this study were taking drugs with known possibility of harm to the development of an unborn child. This was done using four different drug databases.
Results: A subset of 111 patients was not taking hormonal contraceptives (birth control pills or vaginal rings). Of those, 99 patients were taking at least one drug that is not recommended during pregnancy according to at least one of the four databases. Most of the medications taken have the potential to affect normal foetal development.
Conclusion: To ensure safe use of medications, the patients should be reminded of the importance of effective contraception.

Keywords: adverse drug effects, contraception, fertile age, foetal development, multiple sclerosis, pharmacotherapy, women

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Introduction

Approximately 2.8 million people live with multiple sclerosis (MS) worldwide.[1] This makes MS the most frequent neuroimmunological disease of the central nervous system at a relatively young age. MS is widely heterogeneous in terms of symptoms, histology and radiology.[2] The symptoms of MS range from the soft signs, such as fatigue and cognitive changes,[3–5] to paralysis, spasticity,[4] bladder dysfunction and sexual dysfunction.[6,7]

The therapeutic management of MS is complex. As a consequence, MS patients often take several medications, resulting in a relatively high risk of polypharmacy (of up to 59%).[7] MS is treated with disease-modifying drugs (DMDs) to alleviate disease activity and slow down disease progression. DMDs have been shown to reduce disease severity and curb the development of new lesions in the central nervous system. Further therapeutics are used to treat MS symptoms. Roughly 66.5% of female MS patients suffer from comorbidities, which also need to be treated.[3] Moreover, alternative and complementary medicines are used by many patients in addition to prescribed drugs.[8] Many DMDs are not recommended for the use in pregnancy. There are known risks for the foetus when taking DMDs and other drugs during pregnancy.[9,10] The list of possible side effects for foetuses is long and ranges, for example, from congenital heart defects and hydrocephalus when taking teriflunomide to an increased risk of malformation of the vascular system in embryogenesis when using fingolimod.[11,12]

Women are three times more likely to be affected by MS than men and the onset of the disease in women is mostly during the women's childbearing years.[13,14] The initial diagnosis of MS can change the way many patients think about family planning. One-third of MS patients who did not become pregnant after diagnosis reported concerns about the possibility of passing MS to the unborn children. They also see MS as an additional burden on the future parenthood.[15] The rate of unplanned pregnancies in the general population is around 33–41% worldwide.[16–18] Specifically, the respective rate is estimated to be 32% for female MS patients,[19] thus representing a significant risk factor to be considered. The German guidelines on the diagnosis and treatment of MS do not make a general recommendation for contraceptive use, but they do list DMDs under which a safe contraception should be carried out (e.g. alemtuzumab, cladribine, fingolimod, mitoxantrone, ocrelizumab and teriflunomide).[20] There are also official statements in the US Medical Eligibility Criteria for Contraceptive Use recommending contraceptive use for MS patients.[21] When considering the effectiveness of contraceptives, it is important to distinguish between hypothetical effectiveness and actual effectiveness, which could be decreased by inconsequential or inaccurate use.[22]

In this study, we aimed to determine the frequency of the use of medications not recommended during pregnancy in female MS patients of childbearing age. To this end, we analysed whether the patients in our real-world cohort were taking medicines that are known to have a risk of side effects that may affect the development of a foetus. Our study highlights the importance of an adequate therapy management in light of the risk of unplanned pregnancies.

Materials and methods

Patients

The study was performed at the Department of Neurology at the Rostock University Medical Centre (Germany) and at the Neurological Department of the Ecumenical Hainich Hospital Mühlhausen (Germany) between March 2017 and May 2020. At both centres, patients with MS were treated either as outpatients or as hospitalised inpatients, depending on their disease course and disease activity.

For this cross-sectional study, 212 women of childbearing age from 18 to 48 years were included. They were required to have the diagnosis of a clinically isolated syndrome (CIS) or MS according to the revised McDonald criteria.[23] Moreover, women aged above 48 years were not included, as it is assumed that the onset of menopause typically occurs between the ages of 49 and 52 years.[24]

During the waiting period for routine examinations at the clinic, outpatients were asked whether they are willing to participate in the study. Patients who were hospitalised for several days due to changes in therapy, therapeutic side effects or acute/ongoing disease activity were also asked if they are interested to participate.

The Ethics Committees of the Rostock University Medical Centre and of the Physicians' Chamber of Thuringia approved this study (permit numbers A 2014-0089 and A 2019-0048). We conducted this study in accordance with the Declaration of Helsinki.

Collected data

For the patients included, sociodemographic (age, partnership, years of schooling, number of siblings, number of children, employment status, educational status and place of residence), clinical [comorbidities, MS disease course, age at disease onset, disease duration, type of patient care and the degree of disability according to Kurtzke Expanded Disability Status Scale (EDSS)[25]] and pharmacological data (active agent, drug name, type of application and dosage) were gathered by a structured interview, an anamnesis, clinical neurological examinations and a review of medical records.

Following the suggestions by Laroni *et al.*[26] and Marrie *et al.*[27] (International Workshop on Comorbidities in MS), comorbidities were defined based on patient interviews, medical expertise and clinical records.

Drug characterisation

The term 'drug' refers to both individual active agents and combinations of active agents that are marketed as medications. Only those drugs that were actually taken by the patients were included in the analysis. The drugs were classified according to the prescription status, the interval of the drug use and according to the treatment goal.

Prescription status: Prescription (Rx) or over-the-counter (OTC) drugs.

Interval of drug use: Acute drug use (drugs on demand, DOD) or drug use in regular intervals (e.g. weekly or monthly) for long-term treatment of diseases (long-term drugs, LTD).

Therapeutic goal: Immunomodulatory MS drugs (DMDs), symptomatic MS drugs or drugs to treat comorbidities (not related to MS) or drugs for other conditions (e.g. contraception, which here means the use of an oral hormonal contraceptive or the use of vaginal rings at the time of data collection).

Polypharmacy

Polypharmacy was defined as the simultaneous intake of at least five drugs. This definition is most commonly used in the literature.[28]

Assessment of the drugs according to the suitability in pregnancy

The classification of the safety of drugs with regard to their suitability for the use during pregnancy was based on four different sources of information: the Embryotox database,[29,30] the register of the Australian Therapeutic Goods Administration (TGA),[31] the German online portal of summaries of product characteristics (SmPC)[32,33] and the Reprotox database.[34] The drug safety classification took place from June to August 2020. We entered both individual active substances and combinations of active substances in the databases.

Each database is based on a different classification to describe the drug effects (Supplementary Table 1). Each drug was searched in the respective database, and the risk rating was recorded. The following categories were considered to indicate a potentially harmful effect during pregnancy: category red in Embryotox; category B3, C, D and X in TGA; category 2, 3 and 4 in SmPC; category 3 in Reprotox.

Based on the information from each database, we classified the drugs that were used by the patients into the following: (1) no harmful effects for the foetus or newborn are to be expected, (2) the data situation is insufficient and therefore the drug use during pregnancy cannot be recommended and (3) the drug may interfere with the normal development of a foetus.

We then calculated how many women with MS were taking drugs that potentially have harmful effects when used during pregnancy according to at least one database, according to ≥ 2 or ≥ 3 databases or consistently according to all 4 databases. We also calculated how many patients were simultaneously taking two, three, four or more drugs that are categorised as posing a risk to foetal development in at least one database.

Statistics

PASW Statistics 27 (IBM) was used for analysing the sociodemographic, clinical and pharmacological data. Descriptive statistics included frequencies, medians and ranges, and means and standard deviations. The patient cohort was divided into patients using either birth control pills or vaginal rings as contraceptives (PwCo) and patients not using such contraceptives (Pw/oCo) and patients with and without polypharmacy. Two-tailed Student's *t* tests, chi-square tests, Fisher's exact tests and Mann–Whitney *U* tests were used for the comparative analysis of patient groups and a significance level of $\alpha = 0.05$ was set. Using a false discovery rate (FDR)[35] of 5%, the alpha error accumulation caused by multiple testing was corrected.

Results

Clinical and demographic data

The study population consisted of 212 women with an average age of 36.3 ± 7.6 years. Most women were employed (52.8%), skilled workers (60.4%) and living in a partnership (75.5%). One-third of the female patients lived in a rural community (35.9%). Almost 40% of the women with MS were taking five or more medications (39.2%). The mean age at the onset of MS was 27.8 ± 7.2 years, with a median disease duration of 7 years (range, 0–30 years) and a median EDSS score of 2.0 (range, 0.0–8.0). The most common disease course was relapsing–remitting MS (RRMS, 85.8%), followed by secondary progressive MS (SPMS, 7.1%), CIS (6.1%) and primary progressive MS (PPMS, 1.0%). Most women had at least one concomitant disease in addition to MS (60.9%), with the number of concomitant diseases ranging from zero to seven (Table 1).

Use of contraceptives

Among the patients analysed, 101 women (47.6%) reported taking oral contraceptives or using vaginal rings (PwCo group). Polypharmacy was three times more frequent among PwCo than in Pw/oCo (59.4% *versus* 20.7%). PwCo took significantly more medications than Pw/oCo (medians of 5 *versus* 3 medications). This was also reflected by significant differences between PwCo and Pw/oCo with respect to the use of long-term medications, Rx medications, DMDs and comorbidity medications, with PwCo taking significantly more of those medications than Pw/oCo ($p \leq 0.003$). SPMS was more common in PwCo than in Pw/oCo (10.9% *versus* 3.6%). The average EDSS score was significantly higher in PwCo (2.8 *versus* 2.3). PwCo also had significantly more comorbidities than Pw/oCo (chi-square test: $p = 0.009$). There were no other significant differences between the two groups in the dataset (Table 1). For similar comparisons related to the polypharmacy status of the patients, the reader is referred to the Supplementary Tables 2–5.

Risk assessment of medications in terms of the potential harmfulness in pregnancy

The 212 patients took a total of 182 different drugs. The classification of the 182 different medications varied widely across the four databases. The number of drugs classified as potentially harmful during pregnancy per database ranged from 8 (Embryotox) to 149 (SmPC). The number of drugs classified as 'no indication of harmfulness in pregnancy'

Table 1. Sociodemographic, clinical and pharmaceutical data of female MS patients of childbearing age stratified by contraceptive use.

Characteristic	Total patient cohort (*n* = 212)	Patients using contraceptives[a] (*n* = 101)	Patients using no contraceptives[a] (*n* = 111)	*p*
Sociodemographic data				
Age at data acquisition (years), *M* (*SD*) [range]	36.3 (7.6) [19–48]	36.6 (7.0) [19–48]	36.0 (8.1) [19–48]	0.501[t]
School years, median [range]	10 [8–18]	10 [8–14]	10 [8–18]	0.205[U]
Educational level, *n* (%)				
No training	13 (6.1)	3 (3.0)	10 (9.0)	
Skilled worker	128 (60.4)	67 (66.3)	61 (55.0)	0.086[Chi]
Technical college	27 (12.7)	9 (8.9)	18 (16.2)	
University	44 (20.8)	22 (21.8)	22 (19.8)	
Employment status, *n* (%)				
In training	7 (3.3)	3 (3.0)	4 (3.6)	
In studies	5 (2.4)	2 (2.0)	3 (2.7)	
Employed	112 (52.8)	50 (49.5)	62 (55.9)	0.760[Chi]
Unemployed	11 (5.2)	7 (6.9)	4 (3.6)	
Disability pensioned	69 (32.5)	36 (35.6)	33 (29.7)	
Others	8 (3.8)	3 (3.0)	5 (4.5)	
Partnership, *n* (%)				
Single	52 (24.5)	27 (26.7)	25 (22.5)	0.524[Fi]
Any partnership	160 (75.5)	74 (73.3)	86 (77.5)	
Place of residence, *n* (%)				
Rural community	76 (35.9)	35 (34.7)	41 (36.9)	
Provincial town	38 (17.9)	15 (14.9)	23 (20.7)	0.499[Chi]
Medium-sized town	34 (16.0)	16 (15.8)	18 (16.2)	
City	64 (30.2)	35 (34.7)	29 (26.1)	
No. children, *n* (%)				
0	84 (39.6)	43 (42.6)	41 (36.9)	
1	51 (24.1)	24 (23.8)	27 (24.3)	0.861[Chi]
⩾2	77 (36.3)	34 (33.6)	43 (38.8)	
No. siblings, *n* (%)				
0	25 (11.8)	10 (9.9)	15 (13.5)	
1	140 (66.0)	66 (65.3)	74 (66.7)	0.199[Chi]
⩾2	47 (22.2)	25 (24.8)	22 (19.8)	
Clinical data				
Patient care, *n* (%)				
Outpatient	169 (79.7)	76 (75.2)	93 (83.8)	0.128[Fi]
Inpatient	43 (20.3)	25 (24.8)	18 (16.2)	
Age at MS onset (years), *M* (*SD*) [range]	27.8 (7.2) [12–47]	28.1 (6.5) [12–47]	27.5 (7.9) [12–47]	0.497[t]

(Continued)

Table 1. (Continued)

Characteristic	Total patient cohort (*n* = 212)	Patients using contraceptives[a] (*n* = 101)	Patients using no contraceptives[a] (*n* = 111)	*p*
Disease duration (years), median [range]	7 [0–30]	7 [0–30]	6 [0–26]	0.316[U]
EDSS, median [range]	2.0 [0–8]	2.0 [0–8]	2.0 [0–7.5]	**0.022[U]**
Disease course, *n* (%)				
CIS	13 (6.1)	5 (5.0)	8 (67.2)	
RRMS	182 (85.8)	84 (83.2)	98 (88.3)	0.206[Chi]
SPMS	15 (7.1)	11 (10.9)	4 (3.6)	
PPMS	2 (1.0)	1 (1.0)	1 (0.9)	
No. comorbidities, *n* (%)				
0	83 (39.1)	32 (31.7)	51 (45.9)	
1	56 (26.4)	24 (23.8)	32 (28.8)	
2	40 (18.9)	29 (28.7)	11 (9.9)	**0.009[Chi]***
3	18 (8.5)	7 (6.9)	11 (9.9)	
4	9 (4.2)	4 (4.0)	5 (4.5)	
⩾5	6 (2.9)	5 (5.0)	1 (0.9)	
Pharmaceutical data				
Polypharmacy, *n* (%)				
No	129 (60.8)	41 (40.6)	88 (79.3)	**<0.001[Fi]****
Yes	83 (39.2)	60 (59.4)	23 (20.7)	
No. drugs taken, median [range]				
All drugs	4 [0–15]	5 [1–15]	3 [0–11]	**<0.001[U]****
Rx drugs	2 [0–14]	4 [0–14]	2 [0–7]	**<0.001[U]****
OTC drugs	1 [0–6]	1 [0–6]	1 [0–5]	0.753[U]
DOD	0 [0–7]	0 [0–7]	0 [0–4]	0.339[U]
LTD	3 [0–11]	4 [0–11]	2 [0–9]	**<0.001[U]****
DMDs[b]	1 [0–2]	1 [0–2]	1 [0–1]	**0.003[U]***
Symptomatic drugs	1 [0–9]	1 [0–9]	1 [0–5]	0.053[U]
Comorbidity drugs	2 [0–10]	2 [0–10]	1 [0–6]	**<0.001[U]****

CIS, clinically isolated syndrome; DMDs, disease-modifying drugs for MS; DOD, drugs on demand; EDSS, Expanded Disability Status Scale; FDR, false discovery rate; LTD, long-term drugs; MS, multiple sclerosis; n, number of patients; No., number of; OTC, over-the-counter; *p*, p-value; PPMS, primary progressive multiple sclerosis; RRMS, relapsing–remitting multiple sclerosis; Rx, prescription; SD, standard deviation; SPMS, secondary progressive multiple sclerosis; Significance values <0.05 are indicated in bold.
*FDR < 0.05. **FDR < 0.001.
[a]The grouping of patients was based on the use of either birth control pills or vaginal rings as hormonal contraceptives.
[b]The use of methylprednisolone was counted within the DMD category.
[Chi]Chi-squared test.
[Fi]Fisher's exact test.
[t]Two-sample two-tailed Student's *t* test.
[U]Mann–Whitney *U* test.

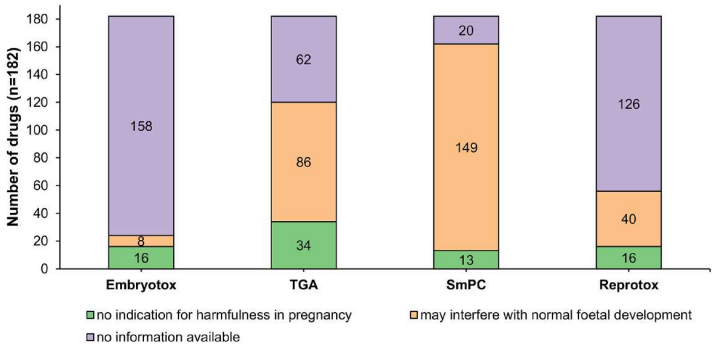

Figure 1. Drug assessment based on databases recording potential effects during pregnancy. A total of 182 different drugs were taken by the MS patients and classified based on different sources of information (Embryotox, TGA, SmPC and Reprotox). The figure shows the proportions of drugs, which were classified as not harmful in pregnancy or potentially interfering with the foetal development. For some drugs, no information was available in the databases.
n, number of drugs; SmPC, summaries of product characteristics; TGA, Therapeutic Goods Administration.

per database ranged from 13 (SmPC) to 34 (TGA) (Figure 1).

A few patients (6.6%) took either no medication ($n=3$) or only medications that were not rated as potentially harmful in any of the four databases used ($n=11$). Conversely, more than 93% of the patients ($n=198$) had at least one drug in their medication plan that is not recommended during pregnancy according to at least one database. In 7.5% of the patients analysed, at least one medication taken was classified as potentially harmful to the foetus in all four databases [Figure 2(a)]. The patients took a median of three drugs that were classified as potentially harmful during pregnancy in at least one database. One in five women (18.4%) took at least five medications classified as potentially harmful in at least one database (Table 2).

Almost all PwCo (98.0%) took at least one medication that was classified as potentially harmful in at least one database [Figure 2(b)]. In Pw/oCo, the respective proportion was significantly lower but still high (89.2%, Fisher's exact test: $p=0.011$). This was also reflected by the fact that PwCo took more medications classified as potentially harmful for the foetus according to at least one database than Pw/oCo (median: 4 *versus* 2, Mann–Whitney U test: $p<0.001$). PwCo were five times more likely to take five or more medications with possible foetal risk according to at least one database than Pw/oCo (31.7% *versus* 6.3%) (Table 2).

Risk classification of drugs frequently used

The most frequently used DMDs were interferon (IFN) beta-1a (12.7%), glatiramer acetate (GA) (12.3%) and fingolimod (9.9%) (Table 3). The most commonly used non-DMDs were cholecalciferol (43.9%), ibuprofen (18.9%) and levothyroxine (14.2%). Three of these six drugs (IFN-beta-1a, fingolimod and ibuprofen) were classified as potentially harmful to the unborn child when taken during (unplanned) pregnancy by two databases. Among the most commonly used drugs, cholecalciferol, immunoglobulin G and magnesium were not found to be potentially harmful during pregnancy in any database. GA, which was classified as potentially harmful only in the SmPC, was used twice as often by Pw/oCo than by PwCo (17.1% *versus* 6.9%, Fisher's exact test: $p=0.035$) A complete list of drugs used with the respective risk classification is given in Supplementary Table 6.

Discussion

The onset of MS in women typically occurs during their childbearing years. Female patients are usually treated with DMDs, some of which carry a teratogenic risk (e.g. fingolimod and

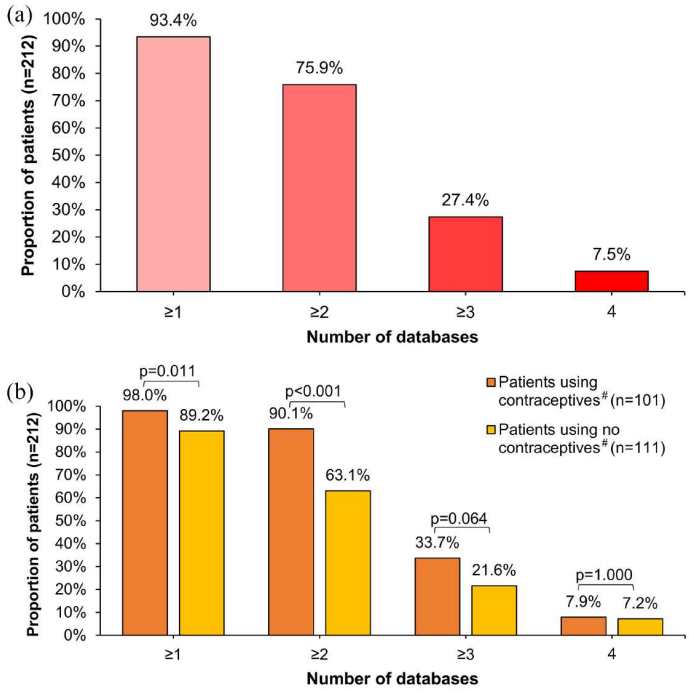

Figure 2. Proportion of female MS patients taking at least one drug not recommended during pregnancy stratified by the level of evidence. Shown is the proportion of women taking at least one drug classified as 'not recommended during pregnancy' stratified by the number of databases (a) for the entire study population ($n = 212$) and (b) for the subgroups PwCo ($n = 101$) and Pw/oCo ($n = 111$). More than 90% of the patients took ⩾1 drug not recommended during pregnancy by ⩾1 of the 4 databases used. Exactly 7.5% of the patients used ⩾1 drug that was consistently classified as potentially harmful for the foetal development in all four databases. PwCo took significantly more often ⩾1 drug with potential harmfulness in pregnancy according to at least one or two databases than Pw/oCo.

n, number of patients; *p*, *p* value (Fisher's exact test); PwCo, patients using contraceptives#; Pw/oCo, patients using no contraceptives#.

#The grouping of patients was based on the use of either birth control pills or vaginal rings as hormonal contraceptives.

teriflunomide).[36] In this study, we performed a comprehensive evaluation of drugs used by women with MS in childbearing age with regard to the potential risk of harmful effects on the unborn child in the case of an unplanned pregnancy. For this purpose, four different evidence-based drug databases were used to assess this risk. Earlier studies provided information about potential influences on the normal foetal development when taking selected medications during pregnancy.[11] The special feature of our study is that we present an assessment of 182 different drugs and that we included both DMDs and non-DMDs (i.e. symptomatic MS therapeutics and comorbidity drugs).

We found that 93.4% of the patients of childbearing age took one or more drugs for which a possible harmful effect on the foetus is indicated in at least one database. Therefore, the use of effective contraceptives is an important issue in the MS treatment management. Hormonal contraception is one of the safest ways to prevent an unintended pregnancy,[37] and in Germany, the 'pill' is the most commonly used contraceptive (47%), followed by male condoms (46%) and intrauterine devices (10%).[38] A previous study reported that 40.0% of the patients with MS used combined oral contraceptives in the past.[39] In our study, the proportion of patients taking birth control pills or vaginal rings was 47.6%. However, as a

Table 2. Proportion of female MS patients taking one or more drugs not recommended during pregnancy according to at least one database.

No. of drugs with potential risk for the foetus	Total patient cohort (*n* = 212)	Patients using contraceptives[a] (*n* = 101)	Patients using no contraceptives[a] (*n* = 111)	p^{Chi}
0	14 (6.6%)	2 (2.0%)	12 (10.8%)	**<0.001****
1	39 (18.4%)	6 (5.9%)	33 (29.7%)	
2	50 (23.6%)	17 (16.8%)	33 (29.7%)	
3	41 (19.3%)	23 (22.8%)	18 (16.2%)	
4	29 (13.7%)	21 (20.8%)	8 (7.2%)	
⩾5	39 (18.4%)	32 (31.7%)	7 (6.3%)	

FDR, false discovery rate; MS, multiple sclerosis; *n*, number of patients; *p*, *p* value.
Shown is the number (percentage) of patients who took none, one or more drugs with potentially harmful effects on the foetus or newborn according to at least one of the four databases used; Significance values <0.05 are indicated in bold.
[a]The grouping of patients was based on the use of either birth control pills or vaginal rings as hormonal contraceptives.
[Chi]Chi-squared test.
**FDR <0.001

limitation, we did not take into account other contraceptive methods. There are multiple reasons for this. On the one hand, we did not ask whether the woman had undergone sterilisation or whether her partner uses condoms for contraception. On the other hand, contraceptives are not regularly listed in the medication plans (due to an insufficient exchange between treating physicians and because some contraceptives, e.g. copper-containing intrauterine devices, are classified as medical devices[40] rather than drugs[41]) and some patients do not disclose their use (often because they do not consider them to be a medication). Therefore, we do not know the exact proportion of patients who did not use contraceptives at all and the individual reasons for this decision.

Although it is recommended in the German guidelines for the treatment of MS that effective contraception should be ensured when administering certain DMDs (e.g. cladribine, fingolimod, mitoxantrone, ocrelizumab or teriflunomide),[20] there are no explicit statements to use or avoid specific contraceptive methods. However, guidelines for the use of contraceptives in MS patients can be found in the US Medical Eligibility Criteria for Contraceptive Use.[21] According to these recommendations, women with MS with prolonged immobility should use levonorgestrel-releasing or copper-containing intrauterine devices (grade 1) rather than combined hormonal contraceptives (grade 3) because of concerns about possible venous thromboembolism, whereas no restrictions apply to women with MS without prolonged immobility.[37] There are also recommendations for contraceptive use at the international level by the World Health Organisation.[42] However, these do not provide any specific guidance for patients with MS.

For long-term therapy planning, physicians should regularly check the patient's desire to have a child. A drug review should be conducted if the patient wishes to become pregnant to evaluate the entire current medication for reproductive toxicity. In particular, the use of DMDs for the treatment of MS in women who wish to become pregnant should always be based on an individual consideration of risks and benefits.[43] There are DMDs for which foetal risks cannot be excluded. Discontinuing the therapy with such DMDs in patients with a desire to become pregnant serves to protect an unborn child from potential consequences on its development.[44–47] For the mother, however, the discontinuation of DMD treatment implicates an increased risk of disease activity in the period up to conception and until after birth, although it has been established that the rate of MS relapses is markedly decreased during pregnancy.[48] Therefore, in women with MS who wish to become pregnant, the use of DMDs that are contraindicated in pregnancy

Table 3. Most frequently used drugs with level of evidence of potentially harmful effects on foetal development during pregnancy.

Drug	Total patient cohort (*n* = 212)	Patients using contraceptives[a] (*n* = 101)	Patients using no contraceptives[a] (*n* = 111)	p^{Fi}	No. of databases indicating potential foetal risk
DMDs					
IFN beta-1a	27 (12.7%)	15 (14.9%)	12 (10.8%)	0.415	2
GA	26 (12.3%)	7 (6.9%)	19 (17.1%)	**0.035**	1
Fingolimod	21 (9.9%)	10 (9.9%)	11 (9.9%)	1.000	2
Alemtuzumab	17 (8.0%)	9 (8.9%)	8 (7.2%)	0.801	1
Methylprednisolone[b]	16 (7.5%)	16 (15.8%)	0 (0.0%)	**<0.001****	2
Natalizumab	16 (7.5%)	12 (11.9%)	4 (3.6%)	**0.035**	2
Dimethyl fumarate	15 (7.1%)	5 (5.0%)	10 (9.0%)	0.293	1
Teriflunomide	14 (6.6%)	5 (5.0%)	9 (8.1%)	0.416	3
Ocrelizumab	8 (3.8%)	7 (6.9%)	1 (0.9%)	**0.029**	3
Immunoglobulin G	7 (3.3%)	3 (3.0%)	4 (3.6%)	1.000	0
Cladribine	4 (1.9%)	2 (2.0%)	2 (1.8%)	1.000	3
Mitoxantrone	3 (1.4%)	1 (1.0%)	2 (1.8%)	1.000	1
Azathioprine	1 (0.5%)	0 (0.0%)	1 (0.9%)	1.000	3
IFN beta-1b	1 (0.5%)	1 (1.0%)	0 (0.0%)	0.476	2
Non-DMDs					
Cholecalciferol	93 (43.9%)	41 (40.6%)	52 (46.8%)	0.407	0
Ibuprofen	40 (18.9%)	19 (18.8%)	21 (18.9%)	1.000	2
Levothyroxine	30 (14.2%)	30 (29.7%)	0 (0.0%)	**<0.001****	1
Magnesium	27 (12.7%)	14 (13.9%)	13 (11.7%)	0.684	0
Pantoprazole	24 (11.3%)	20 (19.8%)	4 (3.6%)	**<0.001****	2
Cyanocobalamin	21 (9.9%)	9 (8.9%)	12 (10.8%)	0.819	1
Enoxaparin	17 (8.0%)	16 (15.8%)	1 (0.9%)	**<0.001****	2
Ethinylestradiol with levonorgestrel	14 (6.6%)	14 (13.9%)	0 (0.0%)	**<0.001****	2
Zopiclone	13 (6.1%)	10 (9.9%)	3 (2.7%)	**0.042**	2
Baclofen	11 (5.2%)	8 (7.9%)	3 (2.7%)	0.122	3
Escitalopram	11 (5.2%)	6 (5.9%)	5 (4.5%)	0.760	2

DMDs, disease-modifying drugs for MS; FDR, false discovery rate; MS, multiple sclerosis; *n*, number of patients; non-DMDs, drugs other than DMDs taken by more than 5% of the patients with MS; *p*, *p* value.
Shown is the number (percentage) of patients using the drug and the number of databases containing the information that the drug may interfere with normal foetal development, with a larger number of databases indicated by a darker red colour; Significance values <0.05 are indicated in bold.
**FDR < 0.001.
[a]The grouping of patients was based on the use of either birth control pills or vaginal rings as hormonal contraceptives.
[b]Quarterly pulse therapy or acute relapse therapy.
[Fi]Fisher's exact test.

might be discontinued in a controlled manner or, depending on the patient's history of disease activity, switched to a therapy with IFN-beta or GA, as these DMDs are considered safe in the first weeks of pregnancy for both the mother and the child.[33]

IFN-beta-1a (which was taken by 12.7% of our patients) and GA (which was taken by 12.3% of our patients) were the most commonly used DMDs in our study. According to the SmPC, there is no evidence of an increased foetal risk when using IFN-beta-1a in the first trimester,[33] but there are insufficient data for the second and third trimesters. The SmPC also states that animal studies suggested an increased risk of spontaneous abortions following IFN-beta administration. However, in humans, no correlation between the use of IFN-beta-1a in early pregnancy and an increased rate of spontaneous abortions was found.[49] Giannini *et al.*[50] reported seven spontaneous abortions in 88 pregnancies exposed to IFN-beta and one spontaneous abortion in 17 pregnancies exposed to GA. The respective risks of spontaneous abortion are comparable to that of the general population.[51] According to the German guidelines[20] and the European guidelines[52] on the pharmacological treatment of MS, the therapy with GA and IFN-beta can be thus continued until pregnancy is confirmed and also continuing this therapy during pregnancy may be considered in some cases if there is a high risk of disease reactivation.

Some experts recommend the same approach when using natalizumab, which received 7.5% of our patients. Accordingly, the therapy with natalizumab might not be stopped until pregnancy is achieved or even until week 34 of pregnancy.[53,54] The patient can be actively involved in such a treatment decision after full discussion of potential implications. However, in our study, we did not ascertain whether some of the patients had consciously decided not to use contraception and to continue the therapy after consulting their doctor. We also did not survey whether the patients would like to receive a better counselling from the neurologist on the use of medications in the context of pregnancy.

Fingolimod and teriflunomide, which were taken by 9.9% and 6.6% of the patients in our study, respectively, carry a potential risk of an abnormal foetal development according to information from the SmPC and TGA. In preclinical studies, fingolimod was found to be associated with an increased teratogenic risk.[55] The use of fingolimod during pregnancy is contraindicated, as a doubled risk of congenital malformations has been shown.[33] Women of childbearing age are therefore advised to use effective contraception methods during fingolimod therapy.[33] After discontinuation of fingolimod, a washout period of at least 2 months prior to conception is recommended.[33] Contraception should be continued during the washout period. In our cohort, there were 9 women taking teriflunomide and 11 women taking fingolimod despite not using oral contraceptives or vaginal rings. Although other contraceptive methods may have been used, this may indicate the need that the treating physician should regularly check that appropriate contraception is being followed in female MS patients of childbearing age.

The timing is an important factor in assessing potential risks to foetuses. This applies, for instance, to the DMDs cladribine and alemtuzumab which are administered in annual treatment cycles and can provide long-term disease control. In our study, a subset of 8.0% and 1.9% of the patients, respectively, were on these DMDs at the time of data collection (i.e. they received a dose within the past year). It is currently advised that conception should not be attempted until at least 6 months after cladribine intake and until at least 4 months after the last dose of alemtuzumab, ideally until the end of the treatment cycle.[20,33] Another example where the duration and frequency of drug administration matters is corticosteroid pulse therapy: 12 of our patients received intravenous methylprednisolone (which has a short half-life) quarterly for 3–5 consecutive days. In our study, we always considered all the drugs in the medication plans, regardless of their time window of action. Our risk assessment is thus overly conservative, which leads to an overestimation of the actual risk of drug exposure and side effects under (unplanned) pregnancy.

In addition to DMDs, many MS patients have to be treated with symptomatic MS drugs and drugs for comorbidities (not related to MS) or other conditions. In our study, 43.9% of the patients took vitamin D supplements in the form of cholecalciferol, albeit there is currently no conclusive evidence for the benefit of cholecalciferol in MS. Some studies reported a reduction in disease

activity,[56,57] whereas other studies failed to identify definitive benefits from the treatment with cholecalciferol in patients with MS.[58,59] The use of cholecalciferol in pregnancy does not need to be restricted according to the information from all four databases used. However, an issue that should not be neglected is the correct and adequate use of cholecalciferol. Prolonged excess of vitamin D intake can lead to intoxication with devastating consequences, such as pancreatitis or kidney failure.[60,61] Approximately 10% of the patients in our study were taking magnesium and cyanocobalamin (vitamin B12), respectively. Interest in such nutritional supplements has increased among MS patients in recent years.[62] Dietary supplements might have a positive influence on the quality of life of MS patients,[63,64] but further clinical trials are needed to gain a deeper understanding of the use of taking dietary supplements in MS.[62]

Ibuprofen was the second most commonly used non-DMD in our study. It is often used in the treatment of MS symptoms.[65] However, patients with MS also use ibuprofen to treat flu-like symptoms that can occur after the administration of IFN-beta preparations.[66] Women becoming aware of their pregnancy are advised to avoid ibuprofen because of the risks it poses for the foetus. Ibuprofen is even contraindicated in the third trimester because it has been associated with foetal renal dysfunction and cardiopulmonary abnormalities according to the SmPC.[33] In this study, we did not distinguish between different levels of risk across the trimesters. It should be noted that, while various medicines are known to have a potentially harmful effect in the first two trimesters, such as carbamazepine and phenprocoumon,[33] there is typically much less data on the safety of drugs in the third trimester, because in clinical studies, the medication is generally stopped when pregnancy is known, and real-world evidence is often limited.

In this study, we used data from four different databases to assess for each drug whether there is a potential risk of harmful effects on unborn children. To our knowledge, no previous study has assessed the potential harmfulness of drugs to foetuses in patients with MS on the basis of multiple databases in a real-world setting. However, the information provided by the individual databases is very heterogeneous in terms of harmfulness and up-to-dateness. Some of the databases are incomplete. For example, the Embryotox database currently lacks some DMDs for the treatment of MS, such as ocrelizumab and cladribine. Because of the different rating scales (Supplementary Table 1), it is rather difficult to make a consistent statement about the harmfulness of each drug to the unborn child.

Focused and frequent consultations between MS patients and treating physicians with regard to medications, side effects and planned pregnancies can be very useful and should be extended. These could improve the use of contraceptives in women with MS to reduce the likelihood of unplanned pregnancies and drug-exposed pregnancies. A review that was composed of information from 25 different randomised controlled trials pointed out the positive effects of motivational interviewing in terms of effective contraception in women.[67] Early planning and open consultations allow for adequate medication changes and necessary washout periods of medications with potential foetal risk. The treating physician should openly discuss the possible risks of Rx and OTC medications in the context of an intended or unplanned pregnancy with the patients. It would also be important to improve the interdisciplinary cooperation between the various specialists, such as family doctors, gynaecologists, pharmacists and neurologists. An early and timely expression of a pregnancy wish allows all specialties to jointly prepare a medication plan that would be well adapted to the needs of the mother and her foetus.

This study has several limitations. Due to the cross-sectional design of this study, we did not capture changes in the patient's medication use over time. Therefore, longitudinal data are needed to conduct further investigations. The limited number of patients impeded to draw firm conclusions on the use of individual drugs or drug combinations in women with MS of childbearing age. Because this study was conducted in Germany, it is also not possible to make generalised statements on the use of DMDs for MS and contraceptives in other countries. We grouped the patients by the use of oral contraceptives or vaginal rings. However, other contraceptive methods, such as transdermal patches, intrauterine devices, female sterilisation

and barrier methods of contraception, were not considered in this work. Of note, in the United States, unlike in Germany,[38] female sterilisation is the most commonly used contraceptive method (with high proportions in women aged 30 years and older), followed by oral contraceptive pills (which are preferred by women below the age of 30 years).[68] Furthermore, the recording of OTC drugs taken was based on the information provided by the patients and may not be accurate due to erroneous omission of medications during the interview. Finally, we focused on women of childbearing age in this study, but male fertility may also be affected by MS medication use, which could be analysed in more detail as well.

Conclusion

In this study, data from four different databases on a wide spectrum of drugs were collected to analyse whether women with MS ($n = 212$) used drugs with known possibility of harm to the development of an unborn child if taken during an (unplanned) pregnancy. We found that 89.2% of the female MS patients who did not use birth control pills or vaginal rings for contraception took at least one medication that was classified as posing a potential risk to the foetus according to at least one database. A percentage of 6.3% of these women were even taking five or more drugs for which at least one database indicated that they may have harmful effects during pregnancy. Furthermore, 7.5% of all women were taking drugs for which potential harmful effects were consistently recorded in all four databases used. An improved communication between neurologists, gynaecologists, pharmacists and the patients is needed to ensure that the use of DMDs fits well with the family planning and is in line with current treatment recommendations for MS. The issue of contraception should be regularly discussed with the patient to prevent an unintended pregnancy and avoid possible drug side effects to mother and child.

Declarations

Ethics approval and consent to participate

The Ethics Committees of the Rostock University Medical Centre and of the Physicians' Chamber of Thuringia approved this study (permit numbers A 2014-0089 and A 2019-0048). We conducted this study in accordance with the Declaration of Helsinki. The study participation of the patients was on a voluntary basis. Informed consent was obtained from all participants in advance.

Consent for publication

Not applicable.

Author contributions

Marie-Celine Haker: Conceptualisation; Formal analysis; Methodology; Resources; Visualisation; Writing – original draft; Writing – review & editing.

Niklas Frahm: Conceptualisation; Data curation; Funding acquisition; Methodology; Supervision; Validation; Writing – review & editing.

Michael Hecker: Conceptualisation; Supervision; Visualisation; Writing – review & editing.

Silvan Elias Langhorst: Data curation; Validation; Writing – review & editing.

Pegah Mashhadiakbar: Data curation; Validation; Writing – review & editing.

Jane Louisa Debus: Writing – review & editing.

Barbara Streckenbach: Data curation; Validation.

Julia Baldt: Data curation; Validation.

Felicita Heidler: Data curation; Validation.

Uwe Klaus Zettl: Conceptualisation; Data curation; Methodology; Validation; Writing – review & editing.

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Competing interests

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Availability of data and materials

The datasets generated and analysed in the current study are available from the corresponding author on reasonable request.

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Supplemental material

Supplemental material for this article is available online.

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9. Abkürzungsverzeichnis

ARR	Annualized relapse rate
CAM	Complementary and alternative medicine
CIS	Clinically isolated syndrome
DDID	Drug-drug interaction databases
DMD	Disease-modifying drugs
EDSS	Expanded Disability Status Scale
GA	Glatirameracetat
IFN-β	Interferon beta
KIDs	Key Potentially Inappropriate Drugs in Pediatrics
MS	Multiple Sklerose
n	Anzahl der Patienten
NEM	Nahrungsergänzungsmittel
OR	Odds ratio
OTC	Over-the-counter
p	p-Wert
pDDI	Potential drug-drug interactions
pDFI	Potential drug-food interactions
PmCo	MS-Patientinnen mit Kontrazeptiva-Gebrauch
PmDDI	MS-Patienten mit mindestens einer Medikamenteninteraktion
PmP	MS-Patienten mit Polypharmazie
PoCo	MS-Patientinnen ohne Kontrazeptiva-Gebrauch
PoDDI	MS-Patienten ohne Medikamenteninteraktion
PoP	MS-Patienten ohne Polypharmazie
PPMS	Primär-progrediente Multiple Sklerose
PwMS	Patienten mit MS
RRMS	Schubförmig-remittierende Multiple Sklerose
Rx	Verschreibungspflichtige Medikamente
SmPC	Summary of medical product characteristics
SPMS	Sekundär-progrediente Multiple Sklerose
TGA	Therapeutic Goods Administration
UAW	Unerwünschte Arzneimittelwirkungen
ZNS	Zentrales Nervensystem

10. Thesen zur Dissertation

1. Die Multiple Sklerose (MS) ist eine chronisch-immunvermittelte Erkrankung des zentralen Nervensystems, die vor allem im jungen Erwachsenenalter diagnostiziert wird. Weltweit zeigte sich eine Zunahme der Prävalenz in den letzten Jahrzehnten (derzeit ca. 2,8 Millionen MS-Patienten).

2. Die Behandlung von Patienten mit MS (PwMS) besteht aus einer komplexen Therapiestrategie. Als verlaufsmodifizierende Therapeutika werden sogenannte Disease-Modifying Drugs (DMD) angewendet. Weitere Therapieelemente stellen die Behandlung von MS-assoziierten Symptomen (z. B. Spastiken), Komorbiditäten und im Real-World Setting Präparate der Komplementär- und Alternativmedizin dar.

3. Der Erkrankungsbeginn der MS fällt oft in die Phase der Familienplanung. Für einige DMD bei MS sowie für Therapeutika von Symptomen oder Komorbiditäten ist eine sichere Kontrazeption empfohlen. Bei Kinderwunsch sollte eine frühzeitige Beratung zur Planung der weiteren Therapie nach mütterlichen und pränatalen Bedürfnissen stattfinden.

4. Polypharmazie beschreibt in der wissenschaftlichen Literatur die gleichzeitige Einnahme von fünf oder mehr Medikamenten.

5. Durch Polypharmazie steigt das Risiko für das Auftreten von potenziellen Medikamenteninteraktionen (potential drug-drug interactions, pDDI), welche zu unerwünschten Arzneimittelnebenwirkungen, verminderten Therapiewirkungen und vermehrten Hospitalisationen führen können und somit auch ökonomisch eine große Bedeutung haben. Zu Beginn dieser Arbeit lagen keine Studien außerhalb der Arbeitsgruppe zu pDDI bei PwMS vor.

6. Ziel der Arbeit war es, die Prävalenz von pDDI bei PwMS und die Assoziation von pDDI mit soziodemographischen, klinischen und pharmazeutischen Daten der PwMS zu untersuchen. Außerdem wurden die verschiedenen Datenbanken hinsichtlich der Detektionsrate und Schweregradbewertung von pDDI miteinander verglichen.

7. Zusätzlich wurden in einer Subgruppe von MS-Patientinnen im gebärfähigen Alter (mit/ohne Kontrazeptiva-Einnahme) die Medikationspläne hinsichtlich potenziell pränatal schädlicher Effekte untersucht und deren Bewertung in Datenbanken zur Arzneimittelsicherheit während einer Schwangerschaft verglichen.

8. Für die Querschnittstudie wurden zu 627 PwMS aus dem Universitätsklinikum Rostock und dem Ökumenischen Hainich Klinikum Mühlhausen soziodemographische und klinische Angaben sowie Medikationsdaten durch eine umfangreiche Datenerhebung erfasst. Die Polypharmazierate lag bei 53,3%.

9. Die Wirkstoffe aus den Medikationsplänen wurden für die Identifizierung von pDDI in drei Interaktionsdatenbanken (*Drugs.com*, *MediQ* und *Stockley´s*) und für die Untersuchung von potenziell pränatal schädlichen Präparaten in vier Datenbanken (*Embryotox, Reprotox, Therapeutic Goods Administration* und deutsche Fachinformationen) eingegeben. Die ermittelten paarweisen pDDI wurden für den jeweiligen Patienten im Medikationsplan vermerkt und anschließend detailliert analysiert.

10. Bei 408 (65,1%) Patienten fand sich mindestens eine pDDI. Die Wahrscheinlichkeit für schwere pDDI war bei Patienten mit Polypharmazie um das 15-fache gegenüber Patienten ohne Polypharmazie erhöht.

11. Als Risikofaktoren für schwere pDDI bei PwMS konnten ein höheres Patientenalter, eine zunehmende Anzahl von eingenommenen Medikamenten, das Vorhandensein von Komorbiditäten und ein geringeres Bildungsniveau gefunden werden.

12. Die verwendeten Interaktionsdatenbanken zeigten heterogene Ergebnisse hinsichtlich der Identifizierung und Schweregradbewertung von pDDI. Nur 18,9% aller pDDI konnten durch alle drei Datenbanken detektiert werden. Der Wirkstoff, für den die meisten schweren pDDI nach zumindest einer der drei Datenbanken gefunden wurde, war Citalopram.

13. In der Untergruppe von 212 Frauen mit MS im gebärfähigen Alter fand sich bei fast 94% der Patientinnen mindestens ein Wirkstoff im Medikationsplan, der laut mindestens einer Datenbank potenziell pränatal toxisch sein kann. Für 7,5% der Patientinnen konnte mindestens ein Medikament gefunden werden, welches nach allen vier Datenbanken ein potenziell schädigenden Effekt auf das ungeborene Kind haben kann.

14. Die drei Studien dieser kumulativen Arbeit stellen erstmalig durch eine umfassende und systematische Analyse an einer großen Patientenkohorte das Ausmaß von pDDI und von potenziell pränatal toxischen Arzneimittelwirkungen bei PwMS dar und liefern damit einen wichtigen Beitrag zur Optimierung der Therapiesicherheit. Die vorliegende Arbeit erweitert die bislang sehr geringe Studiendichte enorm.

15. Zukünftige Längsschnittstudien könnten PwMS unter Berücksichtigung von Medikamentenspiegeln, Arzneimittelnebenwirkungen und korrigierenden Medikamenteneinstellungen analysieren. Dadurch ist eine Steigerung der Aussagekraft hinsichtlich der real auftretenden Komplikationen aufgrund von pDDI und dem tatsächlichen Handlungsbedarf wahrscheinlicher. Intelligentere pDDI-Datenbanken z.B. durch den Einsatz von artifizieller Intelligenz (AI) sind für eine präzisere Anwendung im klinischen Setting notwendig, um zu einer künftig sicheren und individualisierten Pharmakotherapie beizutragen *[Hecker et al., Pharmaceutics, 2023].*

11. Selbstständigkeitserklärung

Ich erkläre hiermit, dass ich die vorliegende Dissertation selbstständig und ohne unerlaubte Hilfe verfasst habe. 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 Jane Louisa Debus

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