Aus der Klinik und Poliklinik für Psychiatrie und Psychotherapie
Klinikum der Ludwig-Maximilians-Universität München
Direktor: Prof. Dr. Peter Falkai

Und dem IFT Institut für Therapieforschung München
Wissenschaftliche Leitung: PD Dr. Eva Hoch

Substanzbezogene Konsumstörungen von Analgetika in Deutschland: Subgruppen unter Konsumierenden von verordneten Opioid-Analgetika sowie Missbrauch von Nichtopioid-Analgetika

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Erster Gutachter:	Prof. Dr. Oliver Pogarell
Zweiter Gutachter:	Prof. Dr. Tobias Dreischulte
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Dekan:	Prof. Dr. med. Thomas Gudermann
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Rauschert, Christian

Name, Vorname

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Abkürzungsverzeichnis

BtMG	Betäubungsmittelgesetz
BtMVV:	Betäubungsmittel-Verschreibungsverordnung
DDD:	Defined Daily Dose (definierte Tagesdosis)
DSM-IV:	Diagnostisches und Statistisches Manual Psychischer Störungen, vierte Version
DSM-5:	Diagnostisches und Statistisches Manual psychischer Störungen, fünfte Version
GKV:	Gesetzliche Krankenversicherung
ICD-10-GM:	Internationale statistische Klassifikation der Krankheiten und verwandter Gesundheitsprobleme, zehnte Revision, German Modification
NOA:	Nichtopioid-Analgetika
OA:	Opioid-Analgetika

Publikationsliste

Publikationen als Bestandteil der vorliegenden Dissertation:

Paper I:

Rauschert C, Seitz N-N, Olderbak S, Pogarell O, Dreischulte T and Kraus L (2022) Subtypes in patients taking prescribed opioid analgesics and their characteristics: A latent class analysis. Front. Psychiatry 13:918371.

Paper II:

Rauschert C, Seitz N-N, Olderbak S, Pogarell O, Dreischulte T and Kraus L (2022) Abuse of non-opioid analgesics in Germany: Prevalence and associations among self-medicated users. Front. Psychiatry 13:864389.

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Beitrag zu den Publikationen

1.1 Beitrag zu Paper I

Der Autor der vorliegenden Dissertation (Christian Rauschert) hat wesentlich zur Konzeption dieses Papers sowie der Studienfrage beigetragen. Er bereitete den Datensatz für sämtliche Analysen vor, führte die statistischen Analysen durch und interpretierte die Ergebnisse. Er schrieb das Originalmanuskript sowie die endgültige Fassung der veröffentlichten Version und begleitete den Publikationsprozess federführend von der Einreichung des Manuskripts im Journal über den Reviewprozess bis hin zur Bearbeitung der Druckfahnen.

1.2 Beitrag zu Paper II

Der Autor der vorliegenden Dissertation (Christian Rauschert) hat wesentlich zur Konzeption dieses Papers sowie der Studienfrage beigetragen. Er bereitete den Datensatz für sämtliche Analysen vor, führte die statistischen Analysen durch und interpretierte die Ergebnisse. Er schrieb das Originalmanuskript sowie die endgültige Fassung der veröffentlichten Version und begleitete den Publikationsprozess federführend von der Einreichung des Manuskripts im Journal über den Reviewprozess bis hin zur Bearbeitung der Druckfahnen.

2. Einleitung

2.1 Schmerzen – ein gesellschaftliches Problem

Schmerzen sind weltweit die häufigste Ursache dafür, weshalb Menschen[1] eine medizinische Behandlung aufsuchen (1, 2). Per Definition ist Schmerz eine komplexe Sinneswahrnehmung, die als eine Art Warnfunktion einer bereits eingetretenen oder drohenden Gewebeschädigung im Körper fungiert. Die Wahrnehmung von Schmerz sowie dessen Intensität sind lediglich subjektiv messbar (3). Aus klinischer Sicht wird zwischen akuten- und chronischen Schmerzen differenziert. Akute Schmerzen können z. B. in Folge von Unfällen, Verletzungen oder Krankheiten auftreten und sind meist nur von kurzer Dauer. Als chronische Schmerzen werden dagegen Schmerzen definiert, die über den Zeitraum der normalen Heilungsdauer hinaus anhalten, häufig wird hierfür eine Zeitspanne von länger als drei bis sechs Monate definiert (4-6). Insbesondere chronische Schmerzen zählen mit einer geschätzten Prävalenz von 20 % in der Erwachsenenbevölkerung weltweit zu den häufigsten Gesundheitsproblemen und sind mit einer erheblichen Verminderung der persönlichen Lebensqualität assoziiert (7, 8). Allein in Deutschland leiden einer Schätzung zufolge etwa 23,3 Millionen Menschen (32,9 %) unter dieser Schmerzform (9). Mit einem Anteil von 15,5 % sind chronische Rückenschmerzen dabei die häufigste Ursache (10). Studien belegen, dass chronische Schmerzen mit einer ganzen Reihe weiterer physischer, psychischer und sozialer Probleme assoziiert sind. Dazu zählen neben einem erhöhten Risiko für Mortalität und Morbidität (11, 12) auch die Entwicklung von Depressionen (13) oder Angststörungen (14). Aber auch Probleme im familiären Umfeld oder Freundeskreis z. B. durch Isolation der schmerzleidenden Personen stellen eine enorme Belastung für Angehörige, Freunde

[1] In dieser Arbeit wird aus Gründen der besseren Lesbarkeit das generische Maskulinum verwendet. Weibliche und anderweitige Geschlechteridentitäten werden dabei ausdrücklich mitgemeint, soweit es für die Aussage erforderlich ist.

sowie die Betroffenen selbst dar (15, 16). Neben den Problemen auf individueller Ebene stellt die hohe Bevölkerungsprävalenz chronischer Schmerzen jedoch auch das Gesundheitssystem vor enorme Herausforderungen. So belaufen sich allein die ökonomischen Kosten chronischer Rückenschmerzen, die durch Krankenausfälle und Frühberentung verursacht werden, auf knapp 12,2 Millionen Euro pro Jahr in Deutschland (17). Die Summe aller direkten und indirekten Kosten, die durch chronische Schmerzen verursacht werden, wird sogar auf 20,5 bis 28,7 Milliarden Euro geschätzt (18). Angesichts dieser Zahlen sowie einem jährlichen Anstieg der Neudiagnosen von Personen mit chronischen Schmerzen um etwa 10 % weltweit wird deutlich, dass es sich hierbei um ein Problem der öffentlichen Gesundheit handelt (8).

Das Interesse an einer adäquaten Schmerzbehandlung ist entsprechend groß, da die Behandlung von Schmerzen essenziell ist, um die physische und psychische Funktionalität und somit auch die Lebensqualität der betroffenen Personen zu verbessern. Ein wichtiger Bestandteil der modernen Schmerztherapie ist die medikamentöse Behandlung von Schmerzen. Dazu werden in erster Linie sogenannte Analgetika (Schmerzmittel) eingesetzt. Diese Analgetika lassen sich hinsichtlich ihrer chemischen und pharmakologischen Wirkweise sowie deren Anwendungsgebiet in die beiden Substanzuntergruppen der Opioid-Analgetika (OA) und Nichtopioid-Analgetika (NOA) einteilen.

Im weiteren Verlauf der vorliegenden Arbeit wird eine getrennte Betrachtung dieser beiden Substanzgruppen hinsichtlich ihrer Definition, Wirkweise, Verbreitung in der Bevölkerung sowie den mit dem jeweiligen Konsum assoziierten Risiken für substanzbezogene Konsumstörungen eingegangen. Schließlich wird aufgezeigt, welche

Forschungsfragen die beiden in dieser Dissertation enthaltenen Publikationen jeweils untersucht haben und welche Forschungslücken geschlossen werden konnten.

2.2 Opioid-Analgetika

OA sind Medikamente, die vorwiegend in der Palliativ- und Akutmedizin zur Behandlung von Patienten mit starken Schmerzen eingesetzt werden (3). Die Substanzgruppe der OA umfasst sowohl natürlich vorkommende Opiate, die aus der Pflanze des Schlafmohns (*Papaver somniferum*) gewonnen werden, wie z. B. Morphin oder Codein als auch die halb- und vollsynthetisch hergestellten Opioide wie z. B. Oxycodon, Methadon oder Fentanyl (19). OA wirken ähnlich wie die körpereigenen Opioide (Endorphine) an verschiedenen Bindestellen im Körper, den sogenannten Opioid-Rezeptoren und beeinflussen somit die Schmerzwahrnehmung und Schmerzunterdrückung (Analgesie) (20). Zu den bekannten Opioid-Rezeptoren zählen u. a. die sogenannten μ-, κ- und δ-Rezeptoren, die allesamt Teil des endogenen Opioid-Systems sind und sich weiter in ihre Subrezeptoren aufgliedern lassen. Für die analgetische Wirkung ist vorwiegend die Bindung an den μ-Rezeptoren verantwortlich (21). Durch die Bindung an den unterschiedlichen Opioid-Rezeptoren im Körper können OA neben ihrer analgetischen Wirkung jedoch auch teilweise unerwünschte physische und psychische Effekte entfalten. Zu diesen Wirkungen zählen u. a. Übelkeit, Schlafprobleme, Obstipation, Atemdepression, aber auch euphorisierende, sedierende, dysphorische sowie halluzinatorische Effekte (22, 23).

Der Großteil der in Deutschland zugelassenen OA sind starkwirksame Schmerzmittel, die im Betäubungsmittelgesetzt (BtMG) geregelt sind und der Betäubungsmittel-Verschreibungsverordnung (BtMVV) unterliegen. Diese starkwirksamen OA sind in Deutschland ausschließlich durch die Ausstellung eines Betäubungsmittelrezeptes durch

einen Arzt erhältlich (24). Ausnahmen davon bilden schwachwirksame OA wie z. B. Dihydrocodein, Codein, Tramadol und Tilidin (vorwiegend in Kombination mit Naloxon), die auf einem normalen ärztlichen Rezept erhältlich sind (21).

2.2.1 Verbreitung des Konsums von Opioid-Analgetika in Deutschland

Trendbeobachtungen lassen einen konstanten Anstieg der Verordnungen von OA über die letzten 25 Jahre in Deutschland erkennen (25-29). So ist eine Zunahme der Prävalenz der OA-Gesamtverordnungen von 4,2 % im Jahr 2006 auf 4,9 % im Jahr 2016 zu beobachten (30). Einer älteren Studie zufolge lag die Prävalenz der OA-Verordnungen im Jahr 2000 noch bei 3,3 % während im Jahr 2010 etwa 4,5 % aller gesetzlich Krankenversicherten in Deutschland eine solche Verordnung erhielten (25). Analysen des Arzneimittelmarktes zeigen darüber hinaus, dass ein Anstieg der zu Lasten der gesetzlichen Krankenversicherung verordneten Tagesdosen von schwach- und stark wirksamen OA von 129 Millionen definierten Tagesdosen (DDD) im Jahr 1996 auf insgesamt 446 Millionen DDD im Jahr 2020 zu verzeichnen ist (31, 32). Dies entspricht einer Steigerung von etwa 246 Prozent (32). Im internationalen Vergleich zählt Deutschland mittlerweile zu einem der Länder mit dem höchsten pro Kopf Konsum von Opioiden (33). Studien zeigen, dass insbesondere die Langzeitverordnung (≥ 3 Monate) dieser Medikamente stark angestiegen ist (30). Ein Großteil dieser Verordnungen entfällt dabei auf Patienten mit chronischen Nichttumorschmerzen (25), obwohl die Evidenz zur Wirksamkeit in dieser Patientengruppe sehr gering ist (34, 35).

2.2.2 Substanzbezogene Konsumstörungen von Opioid-Analgetika

Aufgrund ihrer pharmakologischen Eigenschaften weisen OA ein erhöhtes Risiko für die Entwicklung substanzbezogener Konsumstörungen wie Missbrauch und Abhängigkeit auf (36, 37). Schätzungen zur Prävalenz einer Opioidkonsumstörung unter chronischen Schmerzpatienten, die OA im Rahmen einer ärztlichen Verordnung einnehmen,

schwanken zwischen 20,8 % in Australien (38) über 43,3 % in Frankreich (39) bis hin zu 23,9 % und 44,4 % in den USA (40, 41). In Deutschland wird die Prävalenz einer Opioidkonsumstörung unter Personen, die ihre Medikamente ausschließlich im Rahmen einer ärztlichen Verordnung einnehmen gemäß den Kriterien der fünften Version des Diagnostisch- und Statistischen Manuals psychischer Störungen (DSM-5) (42) auf 21,5 % geschätzt (43). Trotz des hohen Anstiegs der OA-Verordnungen über die vergangenen Jahre kommen Studien basierend auf unterschiedlichen Datenquellen zu dem Schluss, dass in Deutschland keine „Opioid-Epidemie“ vergleichbar mit der in den USA vorliegt (27, 44, 45). Da Missbrauch und Abhängigkeit mit einer ganzen Reihe an negativen gesundheitlichen und sozialen Folgen einhergehen, scheint die hohe Prävalenz in Deutschland dennoch besorgniserregend (46). Evidenzbasierte Empfehlungen hinsichtlich einer sicheren und effektiven Langzeitanwendung von OA liefert in Deutschland die S3-Leitlinie „Langzeitanwendung von Opioiden bei chronischen nichttumorbedingten Schmerzen (LONTS)“ (47). Zu den bekannten Risikofaktoren, die im Zusammenhang mit der Entwicklung einer Opioidkonsumstörung durch verordnete OA stehen, zählen u. a. das Vorliegen einer Alkoholkonsumstörung, der Konsum illegaler Drogen sowie Depressionen oder andere psychische Erkrankungen (35, 43, 48, 49).

Während sich der Großteil der Studien mit der Identifizierung einzelner Risikofaktoren beschäftigt, ist das Wissen um distinkte Subgruppen unter Personen, die OA im Rahmen einer ärztlichen Therapie einnehmen und eine Opioidkonsumstörung aufweisen, eher gering (35). Studien, die sich mit solchen Subgruppenanalysen befasst haben, stammen überwiegend aus den USA, fehlen jedoch bislang für Deutschland. Informationen über distinkte Patientensubgruppen und deren individuelles Risiko für eine Opioidkonsumstörung, könnten als Entscheidungshilfe hinsichtlich der Notwendigkeit und Dauer einer OA-Therapie von chronischen Nichttumorschmerzpatienten in

Deutschland dienen. Schließlich könnten anhand des Wissens über solche Personengruppen gezielte Präventionsstrategien und Handlungsempfehlungen implementiert werden, um die Behandlung chronischer Nichttumorschmerzen noch sicherer zu gestalten (35).

2.3 Nichtopioid-Analgetika

NOA werden vorwiegend zur Behandlung von leichten bis mittelstarken Schmerzen eingesetzt. Gemäß dem WHO-Stufenschema zur Schmerzbehandlung kann es je nach Art und Intensität des zugrunde liegenden Schmerzes sinnvoll sein, eine Kombinationstherapie von NOA und OA anzuwenden (50). NOA bestehen aus einer heterogenen Substanzgruppe, sodass einzelne Präparate je nach Wirkmechanismus neben analgetischen auch antiphlogistische oder antipyretische Eigenschaften aufweisen können (51). Im Gegensatz zu den OA basieren NOA gemäß ihrem Namen nicht auf Opioiden und entfalten ihre Wirkung dementsprechend nicht durch Bindung an den Opioid-Rezeptoren im Körper. Ihre analgetische Wirkung lässt sich vorwiegend auf die sogenannte Cyclooxygenasen-Hemmung zurückführen. Cyclooxygenasen sind Enzyme, welche für die Bildung von Prostaglandinen zuständig sind, die wiederum für die Sensibilisierung der Schmerzrezeptoren im Körper verantwortlich sind (52). Folglich führt eine Hemmung der Prostaglandinsynthese zu einer Schmerzhemmung. Andere Wirkmechanismen können je nach Substanzuntergruppe vorliegen. In Deutschland sind NOA weitgehend ohne ärztliche Verordnung erhältlich, können jedoch ausschließlich in Apotheken (lokal oder online) erworben werden (53). Zu den bekanntesten Vertretern dieser Medikamentengruppe zählt die Gruppe der sogenannten nichtsteroidalen Antirheumatika (z. B. Ibuprofen, Naproxen, Diclofenac etc.) und Paracetamol.

2.3.1 Verbreitung des Konsums von Nichtopioid-Analgetika in Deutschland

NOA sind die am häufigsten eingenommenen Medikamente im Bereich der Selbstmedikation (51). Ergebnissen einer repräsentativen Studie zum Substanzgebrauch in Deutschland zufolge lag die 30-Tage Prävalenz von NOA unter 18- bis 64-Jährigen im Jahr 2021 bei 47,4 %. Dies entspricht hochgerechnet auf die deutsche Erwachsenenbevölkerung in etwa 24,2 Millionen Personen (54). Derselben Studie zufolge lag die 30-Tages-Prävalenz für die tägliche Einnahme dieser Medikamente bei 6,9 %. Eine Analyse des Absatzmarktes von Arzneimitteln in Deutschland zeigt, dass im Jahr 2019 knapp 46,0 % (ca. 706 Millionen. Packungseinheiten) aller verkauften Arzneimittel auf rezeptfreie apothekenpflichtige Medikamente zurückzuführen sind. Davon entfielen allein 9,5 % (67 Millionen Packungseinheiten) auf die fünf am häufigsten konsumierten NOA (55-57). Einer Studie aus dem Jahr 2015 zufolge nehmen etwa 21,4 % der deutschen Wohnbevölkerung mindestens einmal pro Woche eines dieser häufig gebrauchten NOA-Präparate (Aspirin, Diclofenac, Ibuprofen, Naproxen, Paracetamol) ein (56-58). Die Prävalenz für den Konsum auf regelmäßiger Basis (≥ 4Tage pro Woche) liegt den Autoren der Studie zufolge bei 4,5 %.

2.3.2 Substanzbezogene Konsumstörungen von Nichtopioid-Analgetika

Wie bei nahezu allen Medikamenten können auch im Rahmen einer Therapie mit NOA unerwünschte Arzneimittelwirkungen auftreten, wenn diese nicht ordnungsgemäß eingenommen werden. Zu den häufigsten Nebenwirkungen einer nicht ordnungsgemäßen Einnahme dieser Medikamente zählen u. a. gastrointestinale-, kardiovaskuläre-, renale-, hepatische-, zerebrale- sowie pulmonale Beschwerden (57, 59, 60). Die Risiken spezifischer unerwünschter Arzneimittelwirkungen unterscheiden sich dabei je nach zugrunde liegender Substanz sowie deren Wirkmechanismus im Körper. Generell ist das

Risiko für das Auftreten unerwünschter Arzneimittelwirkungen von NOA im Rahmen einer Selbstmedikation deutlich höher im Vergleich zu einer ärztlich verordneten Therapie (61). Einer Publikation basierend auf Daten zu Vergiftungsanfragen des Giftnotrufs in Erfurt zufolge waren die drei häufigsten NOA-Monoexpositionen durch die drei Substanzgruppen Acetylsalicylsäure, Ibuprofen und Paracetamol verursacht. Zudem zeigen die Studienergebnisse einen beträchtlichen Anstieg der NOA-Monoexpositionen in Höhe von 57 % über die Jahre 2003 bis 2012 (57, 62). Eine positive Korrelation der Häufigkeit der eingegangenen Vergiftungsanfragen und den Absatzzahlen der verkauften Packungseinheiten von NOA ist dabei zu erkennen (56).

Aufgrund ihrer einfachen Verfügbarkeit und weiten Verbreitung in der Bevölkerung ist es wichtig zu wissen, wie hoch das Risiko einer missbräuchlichen Einnahme von NOA unter Personen ist, die eine Selbstmedikation betreiben. Studien zur Schätzung der Prävalenz des Missbrauchs von NOA in Deutschland fehlen jedoch, da es keine standardisierte Definition eines Missbrauchs von NOA gibt (57). Informationen über das Ausmaß des NOA-Missbrauchs sowie den assoziierten Risikofaktoren auf Bevölkerungsebene würden es ermöglichen, gezielte Präventionsmaßnahmen zu entwickeln sowie konkrete Handlungsempfehlungen einzuleiten.

2.4 Untersuchte Forschungsfragen

Angesichts der weiten Verbreitung von Analgetika in Deutschland sowie den mit der Einnahme verbundenen Risiken für Missbrauch und Abhängigkeit ist es dringend erforderlich, sowohl das Ausmaß dieser Problematik in der Bevölkerung zu quantifizieren als auch vulnerable Gruppen frühestmöglich zu identifizieren. Vor diesem Hintergrund besteht das übergeordnete Ziel der vorliegenden Dissertation darin, den derzeitigen Kenntnisstand zum Thema substanzbezogene Konsumstörungen von opioiden und

nichtopioiden Analgetika in Deutschland zu vertiefen, um bestmögliche Präventionsstrategien und Interventionsmaßnahmen auf klinischer und gesundheitspolitischer Ebene entwickeln zu können. In die Dissertation gehen zwei Veröffentlichungen mit ein.

Ziel der ersten Publikation war es, distinkte Subgruppen unter Personen zu identifizieren, die OA im Rahmen einer ärztlichen Verordnung einnehmen und ein erhöhtes Risiko für eine Opioidkonsumstörung aufweisen (Forschungsfrage 1) (35). Dazu wurden zunächst Daten des Epidemiologischen Suchtsurvey (ESA) der beiden Erhebungsjahre 2015 und 2021 gepoolt, um eine möglichst große Anzahl an Personen zu erreichen, die OA innerhalb der letzten 12 Monate vor der Befragung per ärztlicher Verordnung eingenommen haben. Der ESA ist eine bevölkerungsrepräsentative Querschnittstudie zum Konsum psychoaktiver Substanzen in Deutschland, die alle drei Jahre durchgeführt wird. Zielpersonen sind deutschsprachige, in Privathaushalten lebende Personen im Alter von 18- bis 64-Jahren (54). Zur Identifizierung der Subgruppen unter Personen, die OA im Rahmen einer ärztlichen Verordnung einnehmen, wurde das statistische Verfahren einer latenten Klassenanalyse durchgeführt. Die Klassifizierung der Gruppen erfolgte anhand von sieben ausgewählten Variablen, die im Zusammenhang mit einem erhöhten Risiko für eine Opioidkonsumstörung verordneter OA stehen. Schließlich wurden statistische Tests durchgeführt, um Unterschiede zwischen den gefundenen Subgruppen hinsichtlich soziodemografischer Variablen und dem Risiko für eine Opioidkonsumstörung zu analysieren.

In einer zweiten Publikation wurde eine Schätzung der 12-Monats-Prävalenz des Missbrauchs von NOA unter selbstmedizierenden Konsumenten in Deutschland vorgenommen (Forschungsfrage 2) (57). Datenbasis bildete der ESA 2015, da

ausschließlich in diesem Erhebungsjahr explizit Informationen zu substanzbezogenen Störungen von NOA abgefragt wurden (63). Missbrauch von NOA wurde gemäß des ICD-10-GM Code F55.2 „Schädlicher Gebrauch nicht -abhängigkeitserzeugender Substanzen“ operationalisiert (64). Schließlich wurden anhand einer multiplen logistischen Regressionsanalyse Risikofaktoren identifiziert, die im Zusammenhang mit einem Missbrauch von NOA stehen.

Die Ergebnisse der beiden Forschungsfragen wurden jeweils in einer internationalen Fachzeitschrift publiziert und finden sich in abgedruckter Form in den Kapiteln 5 und 6 dieser Arbeit.

3. Zusammenfassung:

Hintergrund: Ein elementarer Bestandteil der modernen Schmerztherapie ist die Schmerzbehandlung mit Analgetika. Je nach pharmakologischer Eigenschaft, Wirkweise und Anwendungsgebiet wird zwischen Opioid-Analgetika (OA) und Nichtopioid-Analgetika (NOA) unterschieden. Aufgrund ihrer pharmakologischen Eigenschaften besitzen OA ein erhöhtes Risiko für substanzbezogene Konsumstörungen wie Missbrauch und Abhängigkeit. In Deutschland fehlt es aktuell an Studien zur Identifizierung von Subgruppen unter Patienten die OA per Verordnung einnehmen und ein erhöhtes Risiko für eine Opioidkonsumstörung aufweisen. Da NOA die am häufigsten zur Selbstmedikation verwendeten Medikamente sind und der Missbrauch von NOA mit einer Vielzahl negativer gesundheitlicher Folgen assoziiert ist, sind Untersuchungen über das Ausmaß dieses Problems in Deutschland erforderlich.

Ziele: Das übergeordnete Ziel der vorliegenden Dissertation war es, den aktuellen Kenntnisstand zum Thema substanzbezogene Konsumstörungen von Analgetika in Deutschland zu vertiefen und bestehende Forschungslücken zu schließen. Hierzu wurden explizit zwei Forschungsziele verfolgt: 1) die Identifizierung von Subgruppen unter Personen, die OA per ärztlicher Verordnung einnehmen und ein erhöhtes Risiko für eine Opioidkonsumstörung aufweisen, und 2) eine Schätzung der Prävalenz des Missbrauchs von NOA unter selbstmedizierenden Konsumenten in Deutschland sowie die Identifizierung assoziierter Risikofaktoren. Für die Umsetzung beider Forschungsvorhaben wurden zwei empirische Untersuchungen durchgeführt.

Methodik: In beiden Forschungsvorhaben diente der Epidemiologische Suchtsurvey (ESA) als Datengrundlage. Der ESA ist eine bevölkerungsrepräsentative Längsschnittstudie zum Thema Substanzkonsum und substanzbezogener Störungen psychoaktiver Substanzen in der deutschen Erwachsenenbevölkerung. Für das erste

Forschungsvorhaben wurden die ESA-Daten der beiden Erhebungsjahre 2015 und 2021 gepoolt verwendet (n = 18.250). Die Identifizierung der Subgruppen unter Personen, die OA per ärztlicher Verordnung eingenommen haben, erfolgte anhand einer latenten Klassenanalyse. Schließlich wurden die identifizierten Gruppen hinsichtlich ihrer soziodemografischen Charakteristika sowie der Prävalenz einer Opioidkonsumstörung miteinander verglichen. In dem zweiten Forschungsvorhaben wurden die Daten des ESA 2015 (n = 9.204) analysiert. Die Schätzung der Prävalenz des Missbrauchs von NOA in Deutschland wurde basierend auf der Definition des ICD-10-GM Code F55.2 „Schädlicher Gebrauch nicht-abhängigkeitserzeugender Substanzen“ durchgeführt. Anhand einer multiplen logistischen Regressionsanalyse wurden Risikofaktoren, die mit einem Missbrauch von NOA assoziiert sind, identifiziert.

Ergebnisse: Im Rahmen der ersten Studie wurden insgesamt drei Subgruppen identifiziert, die als *mental gesundheitlich beeinträchtigte Gruppe*, *Polysubstanzgruppe* und *relativ gesunde Gruppe* bezeichnet wurden. Die beiden ersten Gruppen wiesen statistisch signifikant höhere Prävalenzwerte einer Opioidkonsumstörung im Vergleich zur letzten Gruppe auf. Insgesamt verdeutlichen die Ergebnisse, dass Schmerzpatienten, die sich in einer Opioidtherapie befinden keine homogene Personengruppe darstellen, sondern sich vielmehr hinsichtlich ihres Risikos für eine Opioidkonsumstörung unterscheiden. Die Ergebnisse zeigen ebenfalls, dass die Bedürfnisse chronischer Schmerzpatienten häufig über die reine Schmerzbehandlung hinaus gehen und oftmals einen multidisziplinären Behandlungsansatz erfordern. Die Ergebnisse der zweiten Studie zeigten, dass der Missbrauch von Nichtopioid-Analgetika in der bundesdeutschen Erwachsenenbevölkerung weit verbreitet ist. Angesichts einer zunehmenden Selbstmedikation in Deutschland sowie den negativen Folgen, die mit einem Missbrauch verbunden sind, sollte dies als ein Problem der öffentlichen Gesundheit wahrgenommen

werden. Zudem zeigen die Ergebnisse, dass vermehrt Anstrengungen unternommen werden sollten, um das Bewusstsein für dieses Problem in der Bevölkerung zu stärken.

Schlussfolgerung: Zusammenfassend können die Ergebnisse der vorliegenden Dissertation unmittelbare Implikationen für die Entwicklung und Implementierung effektiver Präventions- und Interventionsmaßnahmen sowohl auf klinischer als auch gesundheitspolitischer Ebene liefern. So kann das Wissen über distinkte Patientensubgruppen die OA per Verordnung einnehmen sowie deren Risiko für eine Opioidkonsumstörung dabei helfen, Entscheidungen über die Notwendigkeit und Dauer einer Opioidtherapie bei Patienten mit chronischen Nichttumorschmerzen zu liefern. Gesundheitsdienstleister sollten sich auch der Risikofaktoren eines Missbrauchs von NOA bewusst sein, um frühestmöglich präventive Maßnahmen ergreifen zu können, dies beginnt bereits im Beratungsgespräch in der Apotheke.

4. Abstract (English):

Background: A fundamental component of modern pain management is the treatment of pain with analgesics. A distinction between opioid analgesics (OA) and non-opioid analgesics (NOA) is made because of their pharmacological properties, mode of action, and area of application. The use of OA, due to their pharmacological properties, carries a risk of abuse and dependence. In Germany, studies to identify distinct patient subtypes at risk for prescription opioid use disorder are lacking. Likewise, with NOA the most commonly used drugs for self-medication and the abuse of NOA associated with several negative health consequences, studies of the extent of this problem in Germany are necessary.

Objectives: The overall aim of the present dissertation was to deepen the current knowledge on the topic of substance-related use disorders of analgesics in Germany and to close existing research gaps. Therefore, two particular research objectives were pursued: 1) identify subgroups of patients using prescribed OA who are at risk for prescription opioid use disorder, and 2) estimate the 12-month prevalence of NOA abuse among self-medicated users of these drugs in the German general population and identify risk factors for abuse. Two empirical studies were conducted to implement both research projects.

Methods: In both research projects, the Epidemiological Survey on Substance Abuse (ESA) served as the data basis. The ESA is a population-representative longitudinal study on substance use and substance-related disorders of psychoactive substances in the German adult population. For the first study, ESA data from waves 2015 and 2021 were pooled (n = 18,250). Latent class analysis was applied to identify subgroups among individuals taking prescribed OA. The identified groups were compared concerning their sociodemographic characteristics and their prevalence of prescription opioid use disorder.

The second study analyzed data from the 2015 ESA (n = 9,204). Estimation of the prevalence of the abuse of NOA in Germany was based on the definition of the ICD-10-GM code F55.2 "Abuse of non-dependence-producing substances." Multiple logistic regression analysis was applied to identify risk factors associated with NOA abuse.

Results: The first study identified a total of three subgroups, labeled as *poor mental health group, polysubstance group*, and *relatively healthy group*. The first two groups had statistically significant higher prevalence rates of prescription opioid use disorder compared to the latter group. Overall, the results illustrate that pain patients undergoing opioid therapy are not a homogeneous group of individuals, but rather differ in terms of their risk for prescription opioid use disorder. The results also show that the needs of chronic pain patients are often beyond pain management alone and sometimes require a multidisciplinary approach to treatment. The results of the second study showed that the abuse of NOA is widespread in the German adult population. Given increasing self-medication in Germany and the negative consequences associated with the abuse of NOA, this should be perceived as a public health problem. Furthermore, the results show that increased efforts should be made to raise awareness of this problem in the population.

Conclusion: In summary, the results of this dissertation may provide immediate implications for the development and implementation of effective prevention and intervention measures at both the clinical and public health levels. For instance, knowledge of distinct patient subgroups taking prescribed OA as well as their risk for prescription opioid use disorder can help inform decisions about the need for and duration of opioid therapy in patients with severe non-cancer pain. Healthcare providers should also be aware of the risk factors for the abuse of NOA to be able to take preventive measures as early as possible, starting with a consultation in the pharmacy.

5. Publikation I

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Subtypes in patients taking prescribed opioid analgesics and their characteristics: A latent class analysis

Christian Rauschert[1], Nicki-Nils Seitz[1], Sally Olderbak[1,2], Oliver Pogarell[3], Tobias Dreischulte[4], Ludwig Kraus[1,5,6*]

[1]Department of Epidemiology and Diagnostics, IFT Institut für Therapieforschung, Munich, Germany [2]Department of Psychology, University of Arizona, Tucson, AZ, United States [3]Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-Universität, Munich, Germany [4]Department of General Practice and Family Medicine, Ludwig-Maximilians-Universität, Munich, Germany [5]Department of Public Health Sciences, Centre for Social Research on Alcohol and Drugs, Stockholm University, Stockholm, Sweden [6]Institute of Psychology, ELTE Eötvös Loránd University, Budapest, Hungary

Abstract

Background: Owing to their pharmacological properties the use of opioid analgesics carries a risk of abuse and dependence, which are associated with a wide range of personal, social and medical problems. Data-based approaches for identifying distinct patient subtypes at risk for prescription opioid use disorder in Germany are lacking.

Objective: This study aimed to identify distinct subgroups of patients using prescribed opioid analgesics at risk for prescription opioid use disorder.

Methods: Latent class analysis was applied to pooled data from the 2015 and 2021 Epidemiological Survey of Substance Abuse. Participants were aged 18-64 years and self-reported the use of prescribed opioid analgesics in the last year (n = 503). Seven class-defining variables based on behavioral, mental, and physical health characteristics commonly associated with problematic opioid use were used to identify participant

subtypes. Statistical tests were performed to examine differences between the participant subtypes on sociodemographic variables and prescription opioid use disorder.

Results: Three classes were extracted, which were labeled as *poor mental health group* (43.0%, $n = 203$), *polysubstance group* (10.4%, $n = 50$), and *relatively healthy group* (46.6%, $n = 250$). Individuals within the *poor mental health group* (23.2%, $n = 43$) and the *polysubstance group* (31.1%, $n = 13$) showed a higher prevalence of prescription opioid use disorder compared to those of the *relatively healthy group.*

Conclusion: The results add further evidence to the knowledge that patients using prescribed opioid analgesics are not a homogeneous group of individuals whose needs lie in pain management alone. Rather, it becomes clear that these patients differ in their individual risk of a prescription opioid use disorder, and therefore identification of specific risks plays an important role in early prevention.

Keywords: Opioid analgesics, opioid use disorder, prescription, latent class analysis, epidemiological survey, DSM-5

Introduction

The use of opioid analgesics (OA) is an established component of adequate pain therapy in palliative and acute medicine for patients with severe pain (1). Over the last 25 years, an increase in OA prescriptions can be observed not only internationally in the most affected countries such as the US (2) or Canada (3), but also in Germany (4–7). Based on analyses of German health insurance data, long-term prescriptions (duration ≥3 months) increased by about four percentage points between 2006 and 2015 (8). Studies showed that most of these prescriptions are for patients with chronic non-cancer pain (4), despite evidence on the effectiveness in this patient group is lacking (9). Owing to their pharmacological properties, the use of OA carries the risk of abuse and dependence (10, 11). In Germany, the 1-year prevalence of prescription opioid use disorder (pOUD) among individuals reporting use of opioids prescribed to them by their providers is currently estimated at 21.2% (12). Even though Germany may not currently be affected by an opioid epidemic (6, 13), the high prevalence of pOUD is concerning. Abuse and dependence are associated with a wide range of personal, social, and medical problems and therefore should be prevented (14). The German S3 guideline "Long-term administration of opioids for non-tumor pain" takes this into account and provides evidence-based recommendations to clinicians for appropriate treatment (15).

Among the behavioral, mental, and physical health conditions that are associated with pOUD are co-occurring alcohol use disorder, polysubstance use of illicit drugs (16, 17), depression as well as other psychiatric disorders (12, 16, 18, 19). Although many studies have identified associations between pOUD and single risk factors, little is known about the existence of specific patient subgroups and their individual risk of pOUD. Data-driven approaches to identify such groups have mainly been applied in the US (20–22) but are lacking in Germany. Identifying distinct subtypes of patients taking prescribed OA and

their individual risk of pOUD may inform decisions around the need for and length of opioid use as well as strategies to prevent pOUD in patients with severe non-cancer pain. The aim of this study was to (1) identify distinct subgroups of individuals who used prescribed OA in the past year based on behavioral, mental, and health characteristics and (2) compare the subgroups by risk of pOUD.

Methods

Study design and sample

The data used in this study are from the Epidemiological Survey of Substance Abuse (ESA), a representative cross-sectional study of Germany's general population on the use of substances that is conducted every 3 years [for a detailed description of the methodology and design of the single studies, see (23)]. The ESA sample was drawn from the 18- to 64-year-old German-speaking population living in private households. Random sampling was carried out using a two-stage selection procedure. First, 254 "sample points" (i.e., cities, districts, municipalities) were selected proportionally to their population size. Then individuals living in these communities were randomly selected based on personal addresses from population registers. Data were collected through the use of a questionnaire (paper-pencil, telephone interviews, or online). A weight correction (age, gender, education, federal states, and district size class) based on the Iterative Proportional Fitting Algorithm was used to weight the data (24).

We pooled data from two waves of the ESA—years 2015 (n = 9,204) and 2021 (n = 9,046)—in which information about OA was available, resulting in a total of 18,250 cases (see section Data Analysis for justification of pooling). Of the total sample 10,199 women (55.9%), 8,038 men (44.0%), and 13 who selected other (0.07%) participated in this study with an average age of 38.4 years (SD = 0.12). The ESA was approved by the

ethics committee of the German Psychological Society (DGPs; Reg.- No: GBLK06102008DGPS).

For the present analysis, only individuals reporting the use of OA within the last 12 months and receiving their medication via a prescription from a medical doctor were included. For the remainder of the manuscript, we refer to these persons as patients.

Variables for Latent Class Analysis (pOUD Risk Factors)

A review of the literature on risk factors identified several behavioral, mental, and health characteristics highly associated with pOUD, which were collected in our survey: hazardous alcohol consumption (25), daily smoking (26), consumption of cannabis (27), consumption of other illicit drugs (amphetamines, ecstasy, LSD, heroin and other opioids, cocaine, crack, hallucinogenic mushrooms) (28, 29), depression, psychological treatment (16, 17, 19, 30), and poor physical health status (31). All variables were dichotomized (yes/no). Hazardous alcohol consumption was assessed using the German version of the Alcohol Use Disorder Identification Test, a screening instrument for alcohol-related disorders with a cut-off value of 8 points out of a possible total of 40 points for having a positive screen (32–34). Daily smoking was defined as the consumption of at least one cigarette per day in the last 30 days. Self-reported information about the consumption of cannabis as well as of other illicit drugs was assessed for the last 12 months. Screening for mental health conditions such as depression as well as information on whether a participant was in treatment for mental health problems or had been diagnosed with a mental disorder was achieved using questions from the Munich Composite International Diagnostic Interview (35, 36). According to the World Health Survey (37), self-rated physical health status was measured using a five-point Likert scale ranging from 1, very good, to 5, very bad. To dichotomize the variable poor health status, the first three points

of the scale were summarized and coded as “no,” whereas the last two points of the scale were summarized and coded as “yes.” These variables were used to identify distinct subgroups of individuals reporting the use of prescribed OA.

Selection of External Factors Related to Extracted Classes

The variable of highest interest, pOUD, was assessed using the written version of the Munich Composite International Diagnostic Interview (35, 36). According to the fifth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (38), an opioid use disorder is defined as having occurred if at least two out of 11 criteria have been met in the last 12 months. However, in patients taking prescribed OA under appropriate medical supervision, only nine criteria are applicable as recommended by the DSM-5. Therefore, the criteria “tolerance” and “withdrawal” symptoms are excluded from the DSM-5 diagnosis and were not considered in the analyses in this paper. Further variables to test for class membership were sociodemographic variables including age (metric), gender (male/female; as none of the participants who selected “other” reported OA use), education (low/middle/high), currently employed (yes/no), and net household income (OECD modified equivalence scale) below the poverty threshold (yes/no). The variable education was categorized into three groups according to the International Standard Classification of Education (ISCED) as follows: low (ISCED 1 and ISCED 2), middle (ISCED 3 and ISCED 4), and high (ISCED 5) (39).

Data Analysis

To reach a sample size of $n \geq 500$, which is sufficiently powered for latent class analysis (LCA) (40–42), the data from two ESA waves, years 2015 and 2021, were pooled. Before the data was pooled, it was tested whether the mean levels (or categorical proportions) and relations between all variables included in the LCA, χ^2 tests, and *t*-tests were

comparable between the waves. We found no statistical difference in the correlations between all variables between the waves. Differences in means (continuous variables) and proportions (categorical variables) were tested using independent *t*-tests and χ^2 tests, respectively (for detailed information see **Supplementary Table 1**). No statistically significant differences were found (all *p*-values < 0.132) except for the variable mode of administration (i.e., paper-pencil, telephone, or internet-based) (*p*-value < 0.01). However, this difference was expected due to an increased internet use from 2015 to 2021: 38.4% of the participants answered the ESA questionnaire online in 2015 whilst in 2021 61.6%.

Seven class-defining variables, as described above, were used to delineate subgroups of patients taking prescription OA using LCA. The LCA is a probabilistic model-based approach that uses multivariate categorical data as inputs to identify unobserved, mutually exclusive classes (subgroups of individuals) in a certain population. Membership of an individual in a specific class is based on similarities in individual response behavior to some chosen set of observed variables by calculating class membership probabilities (43, 44). To determine the number of latent classes, five alternative models were run, ranging from one to five classes. A complex mixture term was needed to avoid biased results resulting from the two-stage selection procedure of the ESA. To choose the best model with an optimum number of classes, goodness-of-fit-criteria such as the Akaike Information Criterion (AIC), the Bayesian Information Criterion (BIC), the adjusted Bayesian Information Criterion (aBIC) as well as entropy were used to compare the five models. High entropy, as well as low values of AIC, aBIC, and BIC, indicate a good class solution, where the BIC was considered the best indicator (40, 45). To evaluate the discriminatory power of the models, average class assignment probabilities were determined (45). The selection of the final model was also based on the researchers'

assessment of the interpretability of the results. The LCA estimation was conducted in MPlus 6.12 (46) using maximum likelihood estimation with robust standard errors.

To identify associations between class membership and pOUD as well as sociodemographic factors (described above), statistical tests were performed. Testing for differences between the identified groups was done with χ^2 tests for categorical variables and *t*-tests for continuous variables. An alpha level of 0.05 was considered for statistical significance. All analysis was performed using Stata 15.1 SE (Stata Corp LP; College Station, TX, USA) (47).

Results

Analysis Sample

Data were available for 537 people who reported using prescribed OA in the past year, of which 34 individuals were excluded because of missing values on key variables: pOUD (21 individuals), unemployed (10 individuals), and education according to the ISCED (3 individuals). The final analysis sample was comprised of 503 individuals.

Prevalence distribution of class-defining variables

Information about the weighted prevalence proportions (with listwise deletion of missing data) of the seven class-defining variables is shown in **Table 1**. Depression (60.2%), as well as daily smoking (32.2%), were the most prevalent indicators, whereas the use of other illicit drugs (9.2%) and the use of cannabis (12.9%) showed the lowest prevalence proportions. About one-fifth (18.3%) of the respondents met the criteria for hazardous alcohol consumption, and one quarter (26.7%) reported being treated for mental health problems or a diagnosed mental disorder.

-Table 1-

Identifying Subgroups With LCA

A review of the goodness-of-fit indicators revealed contradictory recommendations regarding the appropriate number of classes. We ultimately decided on the three-class solution because it had the best fit according to two of the fit indices (BIC and aBIC), a better distribution of class prevalence (average class assignment probability was >0.8), and the subtypes were associated with meaningful and clearly distinct subgroups values (**Table 2**). The assumption of conditional independence in all three classes was met (45).

-Table 2-

Estimated class-specific response probabilities indicating patterns of three distinct subgroups of individuals using prescription OA are presented in **Figure 1**. The first class (43.0%, *n* = 203) showed the highest value for poor health (60.1%) of all classes and very low values for cannabis use (6.3%) and other illicit drug use (0.01%). On account of the highest values for depression (95.7%) and psychological treatment (55.4%) compared with the other classes and low to moderate values in all other class-defining variables, this class was characterized as the *"poor mental health group"*.

Response probabilities of individuals in class 2 (10.4%, *n* = 50) were very high in all substance use variables, with cannabis use showing the highest value (89.4%). Although patients in this class showed a high value for depression, this class was defined as the *"polysubstance group"*.

Class 3 (46.6%, *n* = 250) comprised individuals who were less likely to have poor health (10.1%), less likely to be in psychological treatment (0.5%), and less likely to be engaging in hazardous alcohol use (15.2%), cannabis use (0.4%), or the use of other illicit drugs (4.5%). They also had moderate values for daily smoking (23.0%) and depression (33.9%). Thus, the third class was labeled as the *"relatively healthy group"*.

-Figure 1-

Baseline characteristics of extracted subgroups

Information about weighted proportions of sociodemographic data and pOUD over all three subgroups is displayed in **Table 3**. Individuals in the *poor mental health group* were predominantly female (68.9%, *n* = 156) with an average age of 46.0 years (*SD* = 0.93), and the majority had a middle level of education (53.9%, *n* = 104). In this subgroup, 22.4% (*n* = 44) reported having a net household income below the poverty threshold and 34.4% (*n* = 71) were unemployed. Diagnostic criteria for pOUD were met in 23.2% (*n* = 43) of patients.

Patients in the *polysubstance group* were on average 38.4 years old (*SD* = 1.95), and 49.0% (*n* = 24) were female. The level of education in this subgroup was predominantly low (47.0%, *n* = 16), 29.9% (*n* = 11) were unemployed, and 58.6% (*n* = 17) had an income below the poverty threshold. pOUD was detected in 31.1% (*n* = 13) of patients.

The *relatively healthy group* was marked by individuals with an average age of 45.7 years (*SD* = 0.85). More than half of all patients in this subgroup were female (54.2%, *n* = 146), and the majority had a middle level of education (47.9%, *n* = 105). The proportion of unemployed individuals in this subgroup was 17.3% (*n* = 51), and 17.7% (*n* = 32) had a

net household income below the poverty threshold. pOUD occurred in 10.7% (n = 25) of patients.

-Table 3-

Differences Between Subgroups on External Factors

Individuals in the *poor mental health group* showed significantly higher proportions of pOUD compared with the *relatively healthy group* (23.2% vs. 10.7%). Moreover, patients in this subgroup were more likely to be female (68.9% vs. 54.2%) and unemployed (25.5% vs. 17.3%) compared to those in the *relatively healthy group*. A higher proportion of individuals within the *polysubstance group* had a diagnosis of pOUD compared with the *relatively healthy group* (31.1% vs. 10.7%). Additionally, members of this subgroup were more likely to be younger, with a lower level of education (47.0% vs. 11.9%) as well as a net household income below the poverty threshold (58.6% vs. 17.7%) compared with those in the *relatively healthy group*.

Discussion

The present study investigated pooled cross-sectional data from the ESA for the years 2015 and 2021 to identify distinct subgroups of patients using prescribed OA, based on behavioral, mental, and physical health characteristics commonly considered to be relevant to problematic OA use. The study aimed to address differences in the prevalence of pOUD between the single subgroups. Latent class analysis revealed that a three-class model best fitted the data. Subgroups were labeled as *poor mental health group* (43.0%, n = 203), *polysubstance group* (10.4%, n = 50), and *relatively healthy group* (46.6%, n = 250). Testing for group differences indicated that individuals in the *poor mental*

health subgroup as well as individuals in the *polysubstance group* showed a higher prevalence of pOUD compared to the *relatively healthy group*. Furthermore, patients in the *poor mental health group* were more likely to be female and unemployed. Against that, patients of the *polysubstance group* were more likely to be younger, with a lower level of education and a net household income below the poverty threshold. To our knowledge, this is the first study using a model-based approach to identify distinct subgroups of individuals reporting the use of prescribed OA on a population-based level in Germany. The results add further evidence to the knowledge that patients using prescribed OA are a heterogeneous group of individuals, many of whom are likely to have needs beyond pain management alone. It becomes clear that patients using prescribed OAs differ in their individual risk of pOUD.

When interpreting the findings in relation to previously published work, several of the results could be confirmed. For example, Cochran et al. also identified three subtypes of individuals using prescribed OA while analyzing community pharmacy data in southwestern Pennsylvania (20). Subgroups in this study were labeled as hazardous alcohol group, mental health group, and poor health group, and patients in the mental health group showed the highest risk of opioid misuse. Another study performing LCA among individuals using prescribed OA in the US population also identified a group with mental health issues, labeled as the depressed class (22). Patients in this class were more likely to be female which was in coincidence with the findings of the present study. In the same study, the authors found higher rates of pOUD in patients with comorbid psychopathological disorders. A link between mental disorders and a higher risk of pOUD was also found in other studies (17–19, 48, 49). These findings can be confirmed by the results of the present study, by showing a significant relationship between membership of the *poor mental health group* and a positive diagnosis of pOUD compared to the

relatively healthy group. As in the present study individuals in the *poor mental health group* also showed signs of a higher prevalence of unemployment compared to patients in the *relatively healthy group*, this association could be confirmed by previous studies (50, 51).

As mental health problems and physical disorders often exacerbate each other and pain management, more sophisticated interdisciplinary therapy approaches are needed (20, 52, 53). Psychosocial interventions such as cognitive behavioral therapy, in combination with medical pain management, represent an important resource for patients in this subgroup (54). As individuals in this specific subgroup also showed a high prevalence of unemployment, additional linking of these patients to services in the community to address social determinants of health (e.g., vocational services) might be considered for enhancement of treatment (55). Our findings also indicated that individuals in the *poor mental health group* are more likely to be female, therefore gender-specific treatment programs should be considered in an integrated healthcare setting. This might lower the barriers for some individuals to access substance abuse treatment with enhancing overall treatment outcomes (56). Identifying individuals in the poor mental health subgroup might enable early intervention strategies such as referral to specialized care for these patients (20, 57).

Besides mental health problems, the use of illicit drugs as well as alcohol abuse and smoking are also serious problems in pain patients taking prescription OA that are associated with a higher risk of pOUD (16, 19, 58–61). The results of the present study are in line with those of Afshar et al. who also detected a polysubstance group in hospitalized patients with opioid misuse (21). Patients in this subgroup also showed lower socioeconomic status, which could be confirmed by the present result of a very low net household income in the *polysubstance group*. Larger studies with sample sizes reaching

from 19,000 to 26,000 individuals enrolled in substance abuse treatment programs also identified subtypes of individuals using prescribed OA with polysubstance use and therefore match our labeling for this group (62, 63). Patients in this subgroup might require access to comprehensive addiction services, such as professional addiction counseling and therapy, in addition to appropriate pain treatment. Further, the present findings indicate that patients in the polysubstance group differed significantly in sociodemographic factors compared with the *relatively healthy group*. Therefore, we strongly support the recommendation from the German S3 guideline "Medikamentenbezogene Störungen" [Medication-Related Disorders] for early screening for psychosocial and substance use characteristics at the very beginning of opioid therapy (64).

The present findings also identified a large group of patients using prescribed OA showing no noticeable behavioral, mental or physical health characteristics on most of the indicator variables. Due to moderate values on daily smoking and depression, this class was labeled as the *relatively healthy group*. However, these levels of depression and smoking are comparable to the general German population (65, 66). While Green et al. also identified a medically healthy subgroup in their analysis (63), individuals in the present analysis differed in low proportions of substance use (alcohol, cannabis, illicit drugs) and mental health problems. Statistical testing showed that patients in the *relatively healthy group*, relative to the other subgroups, also had the lowest proportion of a positive pOUD diagnosis (10.7%). Individuals in this subgroup reported the use of OA but hardly showed signs of poor health. It may be possible that these individuals had already overcome successful opioid therapy before answering the survey questionnaire. Assuming that pain reduction is the primary concern in these patients and appropriate medication adherence is ensured, this may lower the risk of pOUD.

Limitations

The present findings are subject to several limitations. As the data in the study are based on self-reports, validity is strongly dependent on the response behavior of the individuals interviewed. Biases resulting from lack of memory and response tendencies resulting from social desirability can neither be quantified nor excluded. Regarding the representativeness of the results, it should be noted that, with the present study design, certain population groups are not or hardly reached. These are mainly individuals older than 64 years, homeless people as well as inmates or people who are accommodated in medical institutions (67). The last category primarily concerns palliative patients. In the case of chronic and acute diseases, the influence of possible hospitalization is quite small as the survey periods lasted about 6 months. Future studies should provide a deeper investigation into the variables that may help to predict pOUD. For instance, the duration of exposure, information about the pain condition treated, as well as information about who was the prescriber of the OA (i.e., specialty vs. general medical prescriber). Unfortunately, these questions were not possible to address in the current paper, because this data was not collected in either ESA wave. Because of the pooling of two cross-sectional surveys, the participation of individuals in both ESA surveys cannot be fully excluded. The two-stage random sampling design, however, essentially eliminates this possibility. Finally, there is also the possibility that people misusing their prescribed OA were included in our analysis sample, which might affect our findings regarding patients being treated for pain conditions. Although not completely impossible, the inclusion of individuals misusing opioids under a prescription regime is very unlikely given the rather strict German prescription regulations (64).

Conclusion

The findings of the present study add new evidence to the classification of individuals using prescribed OA and the prevalence of pOUD on a nationally representative level in Germany. Two specific subgroups with a high prevalence of pOUD, labeled as the *poor mental health group* and *polysubstance group* were identified. While individuals in the *poor mental health group* were more likely to be female and unemployed, patients in the *polysubstance group* were marked by younger age with a low level of education and a net household income below the poverty threshold. Clinicians treating patients in opioid therapy should be aware of these specific subtypes and their highly related risk of pOUD during medical history. Using data-based approaches to delineate patient subgroups from different data sources is highly recommended in further research to gain urgently needed insight into subtype characteristics. Stratification of these subtypes enables targeted early intervention from a clinical as well as a public health perspective.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://www.esa-survey.de/ergebnisse/datenzugang.html.

Ethics statement

The studies involving human participants were reviewed and approved by German Psychological Society (DGPs). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.918371/full#supplementary-material

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TABLE 1 | Weighted prevalence proportions of class-defining variables ($n = 503$).

Indicators	*n*	%	95% CI
Hazardous alcohol use	107	18.3%	[14.5; 22.9]
Daily smoking	128	32.2%	[26.9; 38.0]
Cannabis use	65	12.9%	[9.5; 17.4]
Other illicit drug use	37	9.2%	[6.2; 13.5]
Depression	290	60.2%	[54.8; 65.4]
Psychological treatment	138	26.7%	[22.2; 31.7]
Poor health	123	29.9%	[25.2; 35.0]

% = weighted prevalence for age, region, gender and education; 95% CI, 95% confidence interval; Note: Listwise deletion of missing data.

TABLE 2 | Goodness-of-fit-measures and class-specific response probabilities of the five investigated models for deciding the number of classes ($n = 503$).

Number of classes	Goodness-of-fit measures				Estimated class-specific response probability				
	Entropy	AIC	BIC	aBIC	Class 1	Class 2	Class 3	Class 4	Class 5
1	–	–	3701.803	–	1.000	–	–	–	–
2	0.900	3531.960	3595.269	3547.657	0.910	0.985	–	–	–
3	0.723	3409.778	3506.851	3433.847	0.934	0.865	0.897	–	–
4	0.735	3407.447	3538.285	3439.889	0.834	0.842	0.906	0.825	–
5	0.702	3404.796	3569.399	3445.610	0.879	0.686	0.780	0.937	0.875

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; aBIC, adjusted Bayesian Information Criterion.

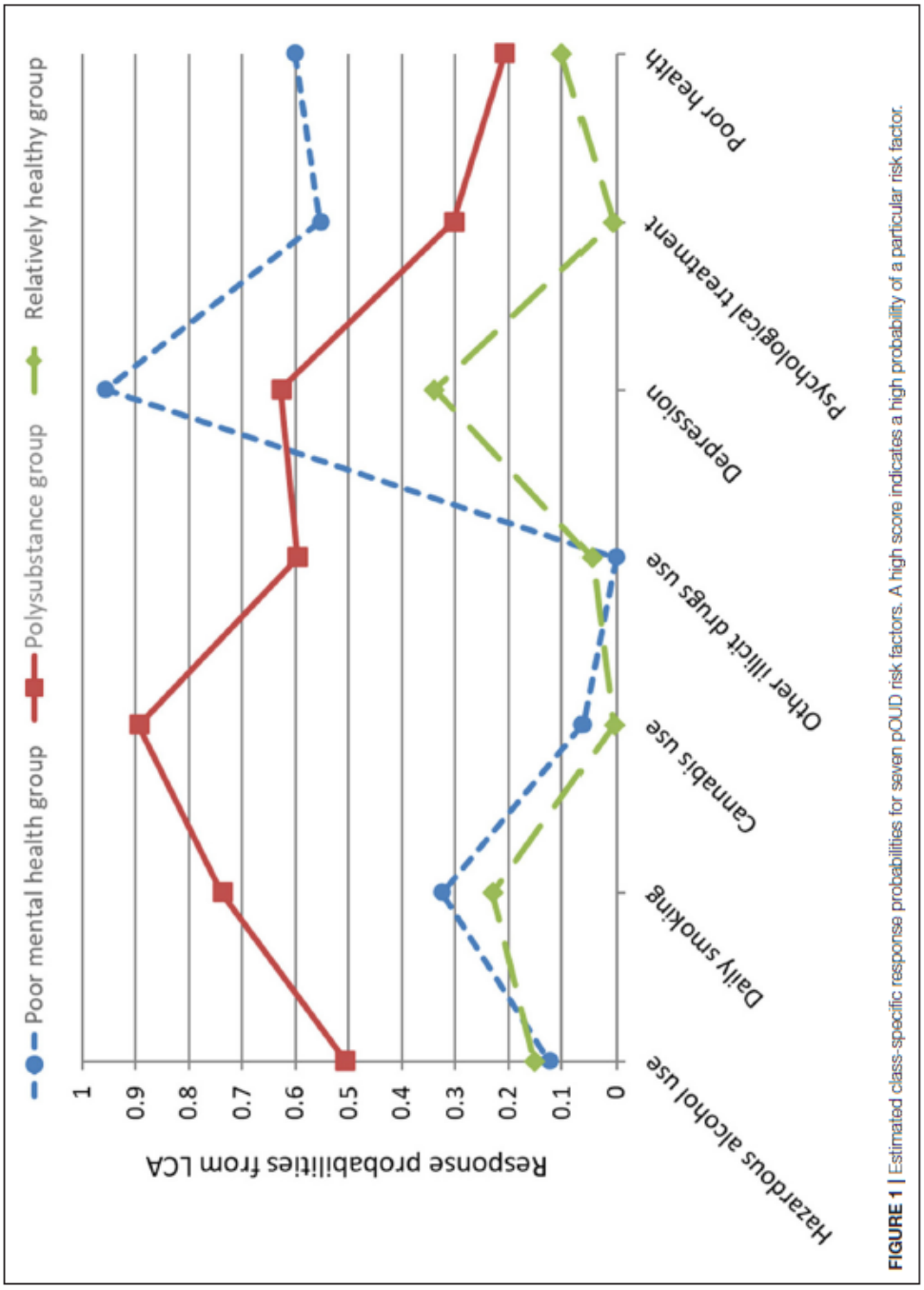

FIGURE 1 | Estimated class-specific response probabilities for seven pOUD risk factors. A high score indicates a high probability of a particular risk factor.

TABLE 3 | Baseline characteristics of the extracted classes.

Indicators		Total sample	Poor mental health group	Polysubstance group	Relatively healthy group
% (*n*)		100.0 (503)	43.0 (203)	10.4 (50)	46.6 (250)
Age	Mean age (SD)	45.1 (0.65)	46.0 (0.93)	38.4 (1.95)	45.7 (0.85)
	p-value	–	0.781[a]	**0.000**[a]	–
Gender	% female (*n*)	60.0 (326)	68.9 (156)	49.0 (24)	54.2 (146)
	p-value	–	**0.009**[a]	0.595[a]	–
Education	% low (*n*)	18.5 (74)	18.7 (34)	47.0 (16)	11.9 (24)
	% middle (*n*)	49.1 (227)	53.9 (104)	34.4 (18)	47.9 (105)
	% high (*n*)	32.5 (202)	27.4 (65)	18.6 (16)	40.3 (121)
	p-value	–	0.050[a]	**0.000**[a]	–
Unemployed	% (*n*)	25.9 (133)	34.4 (71)	29.9 (11)	17.3 (51)
	p-value	–	**0.001**[a]	0.130[a]	–
Income below poverty threshold	% (*n*)	24.0 (93)	22.4 (44)	58.6 (17)	17.7 (32)
	p-value	–	0.359[a]	**0.000**[a]	–
Prescription opioid use disorder	% (*n*)	18.2 (81)	23.2 (43)	31.1 (13)	10.7 (25)
	p-value	–	**0.007**[a]	**0.004**[a]	–

[a]*Comparison of classes: reference group was the relatively healthy group. SD, standard deviation. Note: Percentages are weighted for age, gender, region and education. p-values based on* χ^2*-test for categorial variables and t-test for continuous variables. Bold text denotes statistical significance with* $p < 0.05$.

Table S1. Sociodemographic- behavioral- and health-related characteristics of individuals using prescribed opioid analgesics between the ESA years 2015 and 2021.

Characteristics	ESA 2015 (*n* = 253) % (*n*)	ESA 2021 (*n* = 250) % (*n*)	*p-value*
Age			0.310
Mean (*SD*)	44.4 (0.85)	45.8 (0.96)	
Gender			0.198
Male	36.5 (83)	43.8 (94)	
Female	63.5 (170)	56.2 (156)	
Education			0.289
Low	20.8 (37)	15.9 (37)	
Middle	50.2 (124)	47.8 (103)	
High	29.0 (92)	36.3 (110)	
Unemployed			0.638
Yes	27.1 (68)	24.7 (65)	
No	72.9 (185)	75.3 (185)	
Income below poverty threshold			0.596
Yes	25.2 (49)	22.5 (44)	
No	74.8 (204)	77.5 (206)	
Hazardous alcohol use			0.621
Yes	17.3 (52)	19.4 (55)	
No	82.7 (200)	80.6 (194)	
Daily smoking			
Yes	36.2 (64)	27.7 (64)	0.132
No	63.8 (186)	72.3 (184)	
Cannabis use			0.322
Yes	11.0 (25)	15.1 (40)	
No	89.0 (228)	84.9 (207)	
Other illicit drug use			0.790
Yes	8.8 (17)	9.7 (20)	
No	91.2 (236)	90.3 (228)	
Depression			0.288
Yes	57.5 (130)	63.2 (160)	
No	42.5 (122)	36.8 (88)	
Psychological treatment			0.488
Yes	25.0 (58)	28.4 (80)	
No	75.0 (194)	72.6 (170)	
Poor health			0.682
Yes	30.9 (62)	28.8 (61)	
No	69.1 (190)	71.2 (189)	
Mode of administration			**0.000**
Telephone (CATI)	33.0 (82)	11.3 (26)	
Paper-pencil (PAPI)	43.2 (95)	47.1 (121)	
Internet (CAWI)	23.8 (76)	41.6 (103)	

n = observations; % = weighted prevalence rates; SD = standard deviation;
p-values based on χ^2-test for categorial variables and t-test for continuous variables;
Note: Bold text denotes statistical significance with $p < 0.05$.

6. Publikation II

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Abuse of non-opioid analgesics in Germany: Prevalence and associations among self-medicated useres

Christian Rauschert[1], Nicki-Nils Seitz[1], Sally Olderbak[1,2], Oliver Pogarell[3], Tobias Dreischulte[4], Ludwig Kraus[1,5,6*]

[1]Department of Epidemiology and Diagnostics, IFT Institut für Therapieforschung, Munich, Germany [2]Department of Psychology, University of Arizona, Tucson, AZ, United States [3]Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-Universität, Munich, Germany [4]Department of General Practice and Family Medicine, Ludwig-Maximilians-Universität, Munich, Germany [5]Department of Public Health Sciences, Centre for Social Research on Alcohol and Drugs, Stockholm University, Stockholm, Sweden [6]Institute of Psychology, ELTE Eötvös Loránd University, Budapest, Hungary

Abstract

Background: Abuse of non-opioid analgesics (NOA) is associated with serious health consequences. However, due to inconsistent definitions of NOA abuse, prevalence estimates for the German population are unclear.

Objective: This study aimed to estimate the 12-month prevalence of NOA abuse among self-medicated users of these drugs in the general German population and to identify risk factors.

Methods: Data are from the 2015 Epidemiological Survey of Substance Abuse, a nationally representative sample with 9,204 individuals aged 18–64 years. Classification of NOA abuse was based on self-reported information according to the definition of the ICD-10-GM diagnosis F55.2 abuse of non-dependence producing substances. Multiple logistic regression was performed to examine associations between NOA abuse and sociodemographic, behavioral, and health-related variables.

Results: The weighted 12-month prevalence of NOA abuse was 14.6% (95%-CI [13.2- 16.0]) among self-medicated users of these drugs. Extrapolation of the proportion of individuals abusing NOA to the German population aged 18 to 64 is 3,243,396 individuals or 6.4% (95%-CI [5.7- 7.1]). Inexplicable physical pain, being underweight, depression, hazardous alcohol use, daily smoking, illegal drug use, and frequent use of NOA (one or more times per week and daily use) were associated with an increased probability of NOA abuse. The use of cannabis was associated with a lower probability of NOA abuse.

Conclusion: Abuse of NOA is highly prevalent in the German population. Against the background of increasing self-medication of NOA, healthcare providers need to be aware of potential risk factors of abuse to better identify and prevent this problem.

Keywords: Non-opioid, analgesics, abuse, self-medication, epidemiological survey, over-the counter

Introduction

Non-opioid analgesics (NOA), like non-steroidal anti-inflammatory drugs or antipyretic analgesics such as paracetamol (i.e., acetaminophen), are the most commonly used drugs for self-medication (1). NOA are mainly used for the treatment of mild to moderate acute and chronic pain. In many countries, including Germany, NOA are available without a prescription and are so-called over-the-counter (OTC) medicines. In Germany, NOA can only be purchased in local or online pharmacies, always with the involvement of a pharmacist or a pharmacy technician (2). However, a few OTC drugs, such as vitamin supplements and herbal drugs, are available outside of pharmacies at places like drugstores or supermarkets. In Germany in 2019, 46.9% (or 706 million package units) of all drugs sold (i.e., prescription drugs, OTC pharmacy-only drugs, and drugs available at supermarkets) were OTCs available only in pharmacies. The top five most frequently sold OTC analgesics in 2019 generated a total sale of 67 million package units corresponding to 9.5% of the total sales of all OTC pharmacy-only drugs (3). Of all OTC drugs available only in pharmacies, 83.9% (or 592 million package units) were sold without a medical prescription (4). Analyses of survey data show that 21.4% of the population in Germany take one of the five most common NOA agents (i.e., aspirin, diclofenac, ibuprofen, naproxen, paracetamol) at least once a week, while 4.5% use these analgesics regularly (i.e., four or more days per week) (5).

Besides their positive analgesic effects, NOA also carry the risk of adverse events such as gastrointestinal, cardiovascular, hepatic, renal, cerebral, or pulmonary complications when used inappropriately (6–10). Results of a study of the Poisons Information Center in Erfurt Germany show that the three most frequent single drug exposures of NOA were caused by paracetamol, ibuprofen, and acetylsalicylic acid (11). The number of single

drug exposures of NOA increased from 2003 to 2012 by 57% with a positive correlation between package unit sales and the frequency of exposures. Studies show that the risk of inappropriate use of these drugs is strongly enhanced by self-medication compared to prescribed use (12–14).

As NOA are easily accessible and widely used in the general population, it is important to know their potential for inappropriate use (abuse, or even dependence). In previous literature the terms more often found, and frequently used interchangeably, are *abuse* and *misuse* with several definitions existing for each. In international epidemiological studies, *abuse* is generally defined as the use of NOA for non-medical recreational purposes such as to achieve mind-altering effects (13, 15–19), while *misuse* is largely defined as the use of NOA for a legitimate medical reason but taken in a higher dose or for a period of time longer than recommended (10, 13, 15,16, 20, 21). In other studies, *abuse* has been defined as taking a drug together with another substance, like alcohol (22), or substituting the drug with another one because the drug the individual is dependent on is not available (23). *Misuse* has also been defined as using a medicine for the treatment of symptoms other than the drug is intended (22), or when administering the drug in a manner other than recommended (e.g., intravenous administration instead of oral) (24). Thus, there is a lack of a standardized definition for the abuse and misuse of NOA. In Germany, one study on inappropriate NOA use was limited to a specific form of abuse, namely medication overuse headaches (25), and did not focus on abuse or misuse in general. Another study screened for physical and behavioral dependence on NOA in an elderly hospital population using the fourth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) dependence criteria (26).

Neither the fourth nor the fifth version of the DSM contain a definition of NOA abuse (27, 28). However, the code F55.2 abuse of non-dependence producing substances of the ICD-10-GM coding system (International Statistical Classification of Diseases and Related Health Problems – German Modification) provides a definition that can be used to define NOA abuse (29). According to the ICD-10-GM code F55.2 [F55 in ICD-10-WHO (30)]:

"A wide variety of medicaments and folk remedies may be involved, but the particularly important groups are: (a) psychotropic drugs that do not produce dependence, such as antidepressants, (b) laxatives, and (c) analgesics that may be purchased without medical prescription, such as aspirin and paracetamol.

Persistent use of these substances often involves unnecessary contact with medical professionals or supporting staff and is sometimes accompanied by harmful physical effects of the substances. Attempts to dissuade or forbid the use of the substance are often met with resistance; for laxatives and analgesics, this may be in spite of warnings about (or even the development of) physical harm such as renal dysfunction or electrolyte disturbances. Although it is usually clear that the patient has a strong motivation to take the substance, dependence or withdrawal symptoms do not develop as in the case of the psychoactive substances specified in F10-F19" (29).

The authors were unable to find studies that applied the ICD-10-GM code F55.2 definition to NOA. This may be because there is no standard instrument for the ICD-10-GM diagnoses of NOA abuse that can be applied in epidemiological studies. However, a closer look at the definition of the ICD-10-GM code F55.2, if applied to NOA, reveals that the definition of abuse closely relates to four of the 11 criteria of the DSM-5 for substance use disorder (28).

Based on the ICD-10-GM F55.2 definition of abuse, the present study aimed at estimating the 12-month prevalence of NOA abuse in self-medicated users in the general German population. We also aimed to identify risk factors associated with NOA abuse, to gain knowledge on their association with NOA-related problems.

Material and Methods

Study design and Sample

Data are from the 2015 Epidemiological Survey of Substance Abuse, a population-representative cross-sectional study investigating substance use and substance use disorders among German-speaking 18 to 64-year-olds in the German population. A two-stage selection approach was applied. First, 254 sample points (i.e., cities, districts, municipalities) were randomly selected followed by a random selection of the target population using population registers. Data were collected through a standardized self-report questionnaire that was completed either on paper, through a telephone interview, or online, depending on the preference of the participant. The response rate was 52.2%. The study has been approved by the ethics committee of the German Psychological Society (DGPs; Reg.- No: GBLK06102008DGPS) and a detailed description of the methodology and design of the study can be found here: (31).

The total study sample comprised 9,204 individuals with 49.6% females, 50.4% males, and an average age of 38.3 years (SD = 14.7). For the present analysis, we selected individuals who used NOA in the last 12 months and reported that the NOA were not exclusively prescribed by a medical doctor. The final sample (n = 4,256) is described in the results section below.

Definition of non-opioid analgesics abuse

Abuse of NOA was defined based on the code F55.2 abuse of non-dependence-producing substances of the ICD-10-GM (29). For constructing the dichotomous variable of NOA abuse (yes/no) we used four questions from the Munich Composite International Diagnostic Interview (M-CIDI) that matched the ICD-10-GM definition (32, 33). Individuals that self-reported the use of NOA during the last 12 months were categorized as abusing NOA if they reported to meet one or more of the following criteria: (1) NOA were often taken in larger amounts or over a longer period than intended, (2) a persistent desire or unsuccessful efforts to cut down or control NOA use, (3) continued NOA use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance, or (4) craving, or a strong desire or urge to use NOA.

Participant characteristics and measures

We tested sociodemographic characteristics including age (18 to 24 years, 25 to 39 years, 40 to 59 years, 60 to 64 years), gender (female, male), currently unemployed (yes, no), net household income (OECD modified equivalence scale) below the poverty threshold (yes/no), the size of their municipality [rural (< 5,000 inhabitants), small-town (5,000 to < 20,000 inhabitants), town (20,000 to < 100,000 inhabitants), city (≥ 20,000 inhabitants)], and education (low, middle, high) for association with NOA abuse. The education categories followed the International Standard Classification of Education (ISCED) which were further reduced to three groups: low (ISCED 1 and ISCED 2), middle (ISCED 3 and ISCED 4), and high (ISCED 5) (34).

We also tested behavioral and health characteristics including the following dichotomous variables (yes/no): hazardous alcohol use [i.e., a score of 8 or more on the German version of the Alcohol Use Disorder Identification Test (35–37)], daily smoking (i.e., the consumption of at least one cigarette per day during the last 30 days), consumption of cannabis in the last 12 months, consumption of other illicit drugs (i.e., amphetamines, ecstasy, LSD, heroin and other opioids, cocaine, crack, hallucinogenic mushrooms) in the last 12 months, use of opioid analgesics in the last 12 months, inexplicable physical pain in the last 12 months, and having depression in the last 12 months [screens for depression and inexplicable physical pain were taken from the M-CIDI (32, 33)]. We additionally included frequency responses on NOA use, measured for the last 30 days prior to the survey, categorized into "< one time per week," "one time per week," and "daily use". Based on the participants' height and weight, we included body mass index (BMI), which was calculated according to the definition of the World Health Organization (WHO) (underweight < 18.5 kg/m^2, normal weight 18.5 to < 25 kg/m^2, overweight 25 to < 30 kg/m^2, and obese ≥ 30 kg/m^2) (38).

Statistical analysis

Descriptive statistics were applied to examine the sample and compare participants with and without NOA abuse. Testing for differences between the two groups was done with χ^2 testing. To examine associations between NOA abuse and sociodemographic, behavioral, and health characteristics, we applied multiple logistic regression generating Odds Ratios (OR) and 95%-Confidence Intervals (CI) (39). The mode of administration (i.e., paper-pencil, telephone, online) was included in the model as a control variable. Interactions between NOA abuse and age, sex, education, BMI category, or daily smoking were tested for statistical significance. Inspection of Variance Inflation Factors ensured

that the predictor variables were not collinear. Weights were used to account for sample differences in the distribution of age, gender, and education relative to the population, as well as their representation of the federal states and districts (40). Information on the size of Germany's 18- to 64-year-old population (N = 50,996,806 individuals as of 31.12.2014) (41) was used for a simple projection of the estimated prevalence to the respective total population. Data analysis was performed using Stata 15.1 SE (Stata Corp LP; College Station, TX, United States) (42). An alpha level of 0.05 was considered for statistical significance.

Results

Sample characteristics

Data were available on 4,256 individuals reporting self-medication of NOA. Of these, 218 individuals were excluded due to missing information on key variables resulting in a final analytical sample of 4,038 individuals for the multiple logistic regression model. Baseline characteristics of the final sample are shown in **Table 1**. The majority of participants were female (n = 2,558; 57.1%) with a medium level of education (n = 1,887; 48.8%) and a mean age of 39.7 years. A total of 588 (14.6%) participants reported suffering from inexplicable physical pain and 1,436 (36.0%) individuals reported symptoms of depression.

-Table 1-

Prevalence of non-opioid analgesics abuse

Among all NOA users, 569 individuals met the criteria according to the ICD-10-GM F55.2 diagnosis abuse of non-dependence-producing substances. This corresponds to a weighted 12- month-prevalence of 14.6% (95%-CI [13.2- 16.0]). Extrapolating the proportion of individuals abusing NOA to the German population aged 18 to 64 years yields an estimated number of 3,243,396 individuals or a prevalence of 6.4% (95%-CI [5.7-7.1]). Of the individuals with a diagnosis of NOA abuse 47.1% (n = 276) endorsed item 1 (NOA use in larger amounts or over a longer period than intended), 40.7% (n = 216) endorsed item 2 (persistent desire or unsuccessful efforts to cut down or control NOA use), 58.0% (n = 336) endorsed item 3 (continued NOA use despite knowledge of having persistent or recurrent physical or psychological problems), and 9.9% (n = 69) endorsed item 4 (experiencing a craving or a strong desire or urge to use NOA).

Abuse and non-abuse of non-opioid analgesics by sociodemographic, behavioral, and health-related characteristics

Comparison of sociodemographic, behavioral, and health-related characteristics between individuals abusing NOA and those taking NOA, but not abusing them, are shown in **Table 2**. Individuals abusing NOA showed statistically significant higher rates of unemployment and poverty compared to non-abusers. NOA abusers were more likely to suffer from inexplicable physical pain and depression compared to non-abusers. Further individuals abusing NOA were more likely to be underweight, overweight, or obese and less likely to have a normal BMI value. Additionally, abusers of NOA reported significantly more hazardous alcohol use, daily smoking, illegal drug use, and opioid analgesic use, compared with non-NOA-abusers. Finally, participants abusing NOA also reported a significantly higher frequency of NOA use compared with non-abusers.

-Table2-

Factors associated with non-opioid analgesics abuse

Weighted OR and 95% CIs of the multiple logistic regression model are presented in **Table 3**. The following factors were associated with an increased probability for NOA abuse: inexplicable physical pain (OR = 2.13; 95%-CI [1.64; 2.77]), being underweight (OR = 2.24; 95%-CI [1.24; 4.04]), having depression in the last 12 months (OR = 1.73; 95%-CI [1.34; 2.24]), engaging in hazardous alcohol use (OR = 1.45; 95%-CI [1.09; 1.95]), engaging in daily smoking (OR = 1.34; 95%-CI [1.01; 1.79]), engaging in illegal drug use in the last 12 months (OR = 2.99; 95%-CI [1.41 6.34]), the use of NOA more than one time per week (OR = 2.61; 95%-CI [2.00; 3.41]), and daily NOA use (OR = 3.06; 95%-CI [1.52; 6.18]). The use of cannabis was associated with a lower likelihood of NOA abuse (OR = 0.62; 95%-CI [0.39; 0.99]).

-Table3-

Discussion

We estimated the weighted 12-month-prevalence of NOA abuse among self-medicated users of NOA to be 14.6%, or 6.4% of the 18-64-year-old German population. Inexplicable physical pain, being underweight, having depression, engaging in hazardous alcohol use, smoking daily, using illegal drugs, and frequent use of NOA (i.e., more than once per week) were associated with NOA abuse. In contrast, the use of cannabis was associated with a lowered probability for NOA abuse.

Previous research on non-opioid analgesics abuse

To our knowledge, only three studies have investigated the problematic use of NOA in Germany. One study investigated drug-related problems in the self-medication of OTC drugs, including OTC analgesics, identified by community pharmacists at the time the drug was dispensed (43). Findings of this study showed that the overall prevalence of drug abuse or using the drugs longer than intended was 17.1%, with analgesics the most frequently mentioned drug. The authors additionally reported that the overall prevalence of taking the wrong dosage was 6.8% (43). The second study, a review article, showed that the prevalence of medication overuse headaches (i.e., getting a headache from taking medication to treat a headache for 15 or more days per month) due to analgesics and anti-migraine agents in the general German population ranged from 0.7 to 1.0% (25).

The third study used the criteria of the DSM-IV to screen for physical and behavioral dependence of NOA in an elderly hospital population (26). According to this study, 7% (n = 28) of the patients fulfilled the criteria of NOA dependence. While all patients with a positive diagnosis of NOA dependence showed at least one sign of physical dependence (i.e., tolerance and/or withdrawal symptoms), most of them reported additional behavioral dependence symptoms. Of the participants diagnosed with NOA dependence, 79.2% took "the substance in larger amounts or over a longer period than intended," 91.7% had a "persistent desire or unsuccessful efforts to cut down or control substance use," and 25% continued to take the substance "despite knowledge of having a persistent or recurrent physical or mental problem that is likely to have been caused or exacerbated by the substance" (26, p.268).

To our knowledge, there is only one international study that has investigated NOA abuse specifically. In this study, Kouyanou, Pither (44) investigated 125 chronic pain patients attending specialized pain clinics in South London. The results showed that 48% of the patients were using NOA for pain management. According to the authors, 5.6% of the sample were diagnosed with NOA abuse (i.e., systematic use above the maximum recommended dose for more than one month), and 4% (n = 5) were diagnosed with NOA misuse (i.e., use often, but not systematically, and above the recommended dose) (44).

Most previous studies focused exclusively on inappropriate use of OTC analgesics (15, 45–47). However, because countries differ in terms of which analgesics are classified as OTC medicines, the possible inclusions of non-NOA drugs render comparisons with our study difficult. For example, in some countries (e.g., France, the Netherlands, Poland, the United Kingdom), codeine-combined analgesics (e.g., codeine-ibuprofen) are available as OTC (48). These opioid-containing drugs have a higher risk for abuse and dependence due to their pharmacological properties and were not considered in our study. Additionally, in some countries, like the United States, Poland, or the United Kingdom, NOA are generally easier to obtain than in Germany. For instance, in these countries, OTC analgesics can be purchased in local supermarkets or at gas stations which might create the impression to the public that these drugs are safer than prescription-only drugs, potentially resulting in higher rates of frequent and problematic use (49). Finally, the use of inconsistent definitions of abuse and misuse leads to different results in the estimation of NOA abuse between studies (19, 50). The development of standardized substance abuse terminology is urgently needed to compare prevalence estimates between countries (19).

Risk factors for non-opioid analgesics abuse

When interpreting our findings in light of previously published work, most of the results regarding risk factors could be confirmed. We found the frequent use of NOA (i.e., more than one time per week) to be the strongest predictor of NOA abuse. Findings of a Finnish study showed that frequent use of OTC analgesics is highly related to the frequency of pain symptoms, with a positive association between daily analgesic use and the frequency of pain symptoms (51). Given the fact that the frequent use of these drugs above a certain threshold has no additional positive effect, but rather increases side effects (e.g., medication overuse headache), this might lead to the abuse of NOA in the form of increasing the dose or extending the duration of intake (25, 52, 53).

In accordance with the findings of other studies, our study found daily smoking to be a risk factor for NOA abuse (5, 54, 55). One possible explanation might be that smoking causes many health problems (e.g., rheumatoid arthritis, fibromyalgia), which are associated with having more pain (5, 56–59).

In line with the findings of Abbott and Fraser (23), we found a significant association between hazardous alcohol use and NOA abuse. Wójta-Kempa and Krzyzanowski (45) reported that 26% of users of OTC analgesics consumed these drugs to cure hangovers. Additionally, epidemiological data indicate that the risk for negative health consequences, like gastrointestinal complications, more than double in the case of concurrent use of alcohol and non-steroidal anti-inflammatory drugs compared to the single use of these substances (60). This seems quite concerning considering that Germany is among the top ten countries worldwide with the highest per capita consumption of alcohol (61).

Our results showed a significant positive association between illegal drug use and NOA abuse confirming the findings of Fingleton and colleagues (17) who reported a positive correlation between illegal drug use and OTC medicine abuse in the United Kingdom. An Australian study investigating unintentional deaths attributed to the misuse of OTC analgesics identified the use of additional medications, alcohol, and illicit drugs in 80% of the cases (62).

Most interestingly, in our study cannabis use was associated with a lower probability for NOA abuse. Researchers have shown that cannabis is frequently used, in addition to NOA, for pain management (63, 64). Thus, we attribute this finding to support that, rather than take NOA for pain, participants instead consumed cannabis. Likewise, our finding of the association between inexplicable physical complaints and a higher probability for NOA abuse was not surprising and could be confirmed by previous research (65).

In line with the findings of Benotsch, Koester (18) our results indicate that depression is a strong predictor for NOA abuse. As a previous study showed, depression and chronic pain have a complex relationship with depression occurring more often in patients with chronic pain than in healthy controls (51). Additionally, studies found that some people are using NOA to treat other symptoms than pain, like stress, anxiety, sleep disturbances, and depression (23).

Finally, we found a significant association between being underweight and NOA abuse. This might be explained by the fact that being underweight is associated with chronic pain and is often comorbid with mental disorders like depression (66).

Notes on prevention

Early detection of problematic use of NOA is essential to avoid subsequent harm to the patient. In self-medication, pharmacists play a particularly important role as they can provide direct advice. In Germany, the S3 guideline ‘Medikamentenbezogene Störungen’ of the German Association for Psychiatry and Psychotherapy (DGPPN), in combination with a guideline on drug abuse from the German Federal Chamber of Pharmacists (BAK), provides a good orientation for healthcare providers (67, 68). According to these guidelines, detailed information on the potential risks of medications during consultation is essential. Inquiring about previous medication use, as well as pointing out that these medications should only be used for the recommended period, in addition to a referral to a medical doctor on suspicion of abuse, is essential (67). Further prevention strategies might imply careful screening of patients who receive addiction treatment or cognitive behavioral therapy for alcohol abuse, polysubstance use, or mental health concerns.

Limitations

Our findings are subject to some limitations. All data are based on self-reported information, which is known to be prone to response biases such as underreporting or providing socially desirable answers. Another shortcoming is that with the present cross-sectional study design some population groups with increased rates of substance use are not or are insufficiently covered. This primarily concerns individuals older than 64 years, homeless people, as well as inmates or people who are accommodated in medical institutions (69). A further limitation might be concerning our definition of NOA abuse according to the ICD-10-GM diagnosis F55.2. Because, to our knowledge, there is no valid questionnaire available to assess abuse of NOA according to this definition in population surveys, we used criteria of the M-CIDI according to the DSM-5, and the ICD-

10-GM definition and the DSM-5 criteria are only closely related in meaning. We also chose a conservative approach in setting the threshold to when a participant is characterized into showing abuse or not. As participants only had to fulfill one out of four criteria, it might be that some individuals met only one criterion, even though they are not abusing their drugs. This might have led to an overestimation of NOA abuse. Unfortunately, we were not able to control for individuals suffering from chronic pain (e.g., terminal cancer or rheumatologic patients) who have a permanent need for NOA use, as these variables were not included in the ESA. While the proportion of NOA use without a medical prescription among pain patients may be low, these individuals who regularly need NOA seem to have a high risk for abusing these drugs and we believe are important to include in our study.

Conclusion

The present study provides estimates for NOA abuse in self-medicated users and the German adult population aged 18 to 64 years. Our findings indicate that there is a substantial number of individuals showing signs of abuse according to the definition of the ICD-10-GM. Against the background of increasing self-medication and the fact that abuse of these drugs is strongly associated with negative health consequences, this should be treated as a public health concern. Efforts are needed to raise public awareness about the risks of inappropriate use of these drugs to prevent subsequent harm to NOA users. Several factors were identified that increased the probability of NOA abuse. Healthcare providers should be aware of these risk factors and take early preventive action. Since pharmacists are key in preventing inappropriate use in self-medication, they should explicitly point out potential risks and side effects in consultations with customers. Finally, there is an urgent need to develop a consistent terminology regarding the use,

misuse, and abuse of NOA, in addition to an accompanying operationalization and measurement instrument. These measurement tools are needed to better identify the mechanisms underlying inappropriate use of these drugs and thus better target prevention strategies at an early stage.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://www.esa-survey.de/ergebnisse/datenzugang.html. Further enquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by German Psychological Society (DGPs). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

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

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Table 1. Sociodemographic, behavioral- and health-related characteristics of individuals using NOA and individuals included in multiple logistic regression analysis.

Characteristics	User of NOA (n = 4,256)	Respondents included in multiple logistic regression model (n = 4,038)
	n (%)	n (%)
Age group, years		
18 to 24	1,132 (13.2)	1,093 (13.5)
25 to 39	1,465 (35.7)	1,397 (36.0)
40 to 59	1,420 (45.7)	1,332 (45.4)
60 to 64	239 (5.4)	216 (5.2)
Mean (*SD*)	39.9 (0.2)	39.7 (0.2)
Gender		
Male	1,556 (42.6)	1,480 (42.9)
Female	2,700 (57.4)	2,558 (57.1)
ISCED		
Low	436 (11.2)	402 (10.6)
Middle	1,975 (48.6)	1,887 (48.8)
High	1,830 (40.3)	1,749 (40.6)
Not reported	15	-
Unemployed		
Yes	716 (13.0)	694 (13.0)
No	3,491 (87.0)	3,344 (87.0)
Not reported	49	-
Poverty		
Yes	475 (11.2)	434 (10.4)
No	3,781 (88.8)	3,604 (89.6)
Municipality size		
Rural[a]	178 (4.4)	168 (4.3)
Small town[b]	310 (7.4)	299 (7.6)
Town[c]	833 (19.7)	788 (19.8)
City[d]	2,935 (68.6)	2,783 (68.3)
Inexplicable physical pain		
Yes	627 (14.7)	588 (14.6)
No	3,618 (85.3)	3,450 (85.4)
Not reported	11	-
Body Mass Index (BMI)		
Underweight (< 18.5 kg/m^2)	142 (2.3)	138 (2.4)
Normal (18.5 to < 25 kg/m^2)	2,418 (49.7)	2,314 (50.1)
Overweight (25 to < 30 kg/m^2)	1,129 (31.6)	1,064 (31.6)
Obese (≥ 30 kg/m^2)	567 (16.4)	522 (15.9)
Depression		
Yes	1,519 (36.3)	1,436 (36.0)
No	2,725 (63.7)	2,602 (64.0)
Not reported	12	-
Hazardous alcohol use		
Yes	952 (19.7)	903 (19.4)
No	3,272 (80.3)	3,135 (80.6)
Not reported	32	-
Daily smoking		
Yes	652 (19.9)	601 (19.2)

Table 1 (Continued)

No	3,574 (80.1)	3,437 (80.8)
Not reported	30	-
Illegal drug use		
Yes	96 (2.0)	89 (2.0)
No	4,150 (98.0)	3,949 (98.0)
Not reported	10	-
Cannabis use		
Yes	442 (7.6)	411 (7.3)
No	3,814 (92.4)	3,627 (92.7)
Opioid analgesic use		
Yes	134 (3.5)	123 (3.2)
No	4,096 (96.5)	3,915 (96.8)
Not reported	26	-
Frequency NOA		
< 1 time per week	3,215 (73.4)	3,095 (73.8)
≥ 1 time per week	919 (23.8)	865 (23.5)
Daily use	87 (2.9)	78 (2.7)
Not reported	35	-
NOA abuse		
Yes	569 (14.6)	523 (14.0)
No	3,669 (85.4)	3,515 (86.0)
Not reported	18	-
Mode of administration		
Telephone (CATI)	1,264 (29.0)	1,231 (30.0)
Paper-pencil (PAPI)	1,548 (38.6)	1,380 (35.9)
Internet (CAWI)	1,444 (32.4)	1,427 (34.1)

N = observations; % = weighted prevalence rates; NOA = non-opioid analgesics; ISCED = International Standard Classification of Education. [a] = < 5,000 inhabitants; [b] = 5,000 to < 20,000 inhabitants; [c] = 20,000 to < 100,000 inhabitants; [d] = ≥ 100,000 inhabitants.

Table 2. Sociodemographic- behavioral- and health-related characteristics of abuser and non-abuser of NOA.

Characteristics	Non-abuser of NOA (*n* = 3,515) *n* (%)	Abuser of NOA (*n* = 523) *n* (%)	*χ2*	*(df)*	*p-value*
Age group, years			22.2	(3)	0.072
18 to 24	950 (13.6)	143 (12.6)			
25 to 39	1,230 (36.8)	167 (31.0)			
40 to 59	1,146 (44.4)	186 (51.3)			
60 to 64	189 (5.2)	27 (5.0)			
Gender			0.23	(1)	0.806
Male	1,299 (43.0)	181 (42.3)			
Female	2,216 (57.0)	342 (57.7)			
ISCED			19.89	(2)	0.096
Low	336 (10.2)	66 (13.5)			
Middle	1,646 (48.5)	241 (50.5)			
High	1,533 (41.3)	216 (36.0)			
Unemployed			14.96	(1)	**0.028**
Yes	587 (12.4)	107 (16.3)			
No	2,928 (87.6)	416 (83.7)			
Poverty			41.55	(1)	**0.003**
Yes	361 (9.5)	73 (15.5)			
No	3,154 (90.5)	450 (84.5)			
Municipality size			9.06	(3)	0.472
Rural[a]	147 (4.5)	21 (3.1)			
Small town[b]	264 (7.8)	35 (6.4)			
Town[c]	677 (19.7)	111 (20.7)			
City[d]	2,427 (68.1)	356 (69.8)			
Inexplicable physical pain			268.96	(1)	**0.000**
Yes	433 (12.1)	155 (29.7)			
No	3,082 (87.9)	368 (70.3)			
Body Mass Index (BMI)			34.53	(3)	**0.021**
Underweight (< 18.5 kg/m^2)	114 (2.2)	24 (3.9)			
Normal (18.5 to < 25 kg/m^2)	2,034 (51.1)	280 (44.1)			
Overweight (25 to <30 kg/m^2)	929 (31.4)	135 (32.7)			
Obese (≥ 30 kg/m^2)	438 (15.4)	84 (19.3)			
Depression			223.21	(1)	**0.000**
Yes	1,156 (33.0)	280 (54.8)			
No	2,359 (67.0)	243 (45.2)			
Hazardous alcohol use			25.00	(1)	**0.009**
Yes	766 (18.5)	137 (24.5)			
No	2,749 (81.5)	386 (75.5)			
Daily smoking			64.31	(1)	**0.000**
Yes	494 (17.8)	107 (27.4)			
No	3,021 (82.2)	416 (72.6)			
Illegal drugs use			56.97	(1)	**0.000**
Yes	64 (1.5)	25 (4.7)			
No	3,451 (98.5)	498 (95.3)			
Cannabis use			0.11	(1)	0.845
Yes	354 (7.2)	57 (7.5)			
No	3,161 (92.8)	466 (92.5)			
Opioid analgesic use			82.85	(1)	**0.000**
Yes	87 (2.6)	36 (7.5)			

Table 2 (Continued)

No	3,428 (97.4)	487 (92.5)			
Frequency NOA			407.24	(2)	**0.000**
< 1 time per week	2,806 (77.4)	289 (51.2)			
≥ 1 time per week	657 (20.5)	208 (41.8)			
Daily use	52 (2.0)	26 (7.0)			
Mode of administration			3.32	(2)	0.632
Telephone (CATI)	1,077 (30.1)	154 (29.4)			
Paper-pencil (PAPI)	1,190 (35.5)	190 (38.1)			
Internet (CAWI)	1,248 (34.4)	179 (32.5)			

n = observations; % = weighted prevalence rates. NOA = non-opioid analgesics; ISCED = International Standard Classification of Education. [a] = < 5,000 inhabitants; [b] = 5,000 to < 20,000 inhabitants; [c] = 20,000 to <100,000 inhabitants; [d] = ≥ 100,000 inhabitants. Text in bold face denotes statistical significance with $p < 0.05$.

Table 3. Multiple logistic regression model for factors associated with NOA abuse among user of NOA (n = 4,038).

	Abuse of NOA		
	OR	*p-Value*	*(95% CI)*
Age group, years			
18 to 24	*Ref.*		
25 to 39	0.96	0.799	(0.70-1.32)
40 to 59	1.34	0.092	(0.95-1.88)
60 to 64	1.15	0.651	0.63-2.09)
Gender			
Male	*Ref.*		
Female	0.88	0.353	(0.68-1.15)
ISCED			
Low	*Ref.*		
Middle	1.02	0.951	(0.61-1.69)
High	1.02	0.948	(0.58-1.79)
Unemployed			
Yes	1.11	0.558	(0.82.1.86)
No	*Ref.*		
Poverty			
Yes	1.24	0.303	(0.82-1.86)
No	*Ref.*		
Municipality size			
Rural[a]	*Ref.*		
Small town[b]	1.10	0.809	(0.49-2.48)
Town[c]	1.71	0.102	(0.90-3.25)
City[d]	1.59	0.139	(0.86-2.92)
Inexplicable physical pain			
Yes	**2.13**	**0.000**	**(1.64-2.77)**
No	*Ref.*		
Body Mass Index (BMI)			
Underweight (< 18.5 kg/m^2)	**2.24**	**0.008**	**(1.24-4.04)**
Normal (18.5 to < 25 kg/m^2)	*Ref.*		
Overweight (25 to < 30 kg/m^2)	1.01	0.958	(0.75-1.36)
Obese (≥ 30 kg/m^2)	1.07	0.651	(0.79-1.46)
Depression			
Yes	**1.73**	**0.000**	**(1.34-2.24)**
No	*Ref.*		
Hazardous alcohol use			
Yes	**1.45**	**0.012**	**(1.09-1.95)**
No	*Ref.*		
Daily smoking			
Yes	**1.34**	**0.044**	**(1.01-1.79)**
No	*Ref.*		
Illegal drugs use			
Yes	**2.99**	**0.005**	**(1.41-6.34)**
No	*Ref.*		
Cannabis use			
Yes	**0.62**	**0.043**	**(0.39-0.99)**
No	*Ref.*		
Opioid analgesic use			
Yes	1.41	0.242	(0.79-2.53)

Table 3 (Continued)

No	*Ref.*		
Frequency NOA			
< 1 time per week	*Ref.*		
≥ 1 time per week	**2.61**	**0.000**	**(2.00-3.41)**
Daily use	**3.06**	**0.002**	**(1.52-6.18)**
Mode of administration			
Telephone (CATI)	*Ref.*		
Paper-pencil (PAPI)	1.04	0.802	(0.76-1.43)
Internet (CAWI)	1.00	0.982	(0.73-1.35)

OR: weighted Odds ratio; 95%-CI: 95% confidence interval; Ref.: reference category; NOA= non-opioid analgesics; ISCED= International Standard Classification of Education. [a] = <5,000 inhabitants; [b] = 5,000 to < 20,000 inhabitants; [c] = 20,000 to < 100,000 inhabitants; [d] = ≥ 100,000 inhabitants. Text in bold face denotes statistical significance with $p < 0.05$.

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