PSYCHOLOGISCHE ASPEKTE DER BLUTHOCHDRUCKBEHANDLUNG

Einstellungen, Placebo- & Noceboeffekte

Dissertation

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INHALTSVERZEICHNIS

1 ZUSAMMENFASSUNG UND ABSTRACT

1.1 Zusammenfassung

Bluthochdruck ist eine weit verbreitete Erkrankung, die häufig eine medikamentöse Kontrolle des Blutdrucks erfordert, um Folgeerkrankungen vorzubeugen (Kearney et al., 2005). Die Adhärenz bei Bluthochdruckmedikamenten, also in wie weit Patienten dem Behandlungsplan folgen, ist niedrig (Naderi, Bestwick, & Wald, 2012). Zur Verbesserung der Behandlung sollten erwünschte, unspezifische Effekte der Bluthochdruckmedikation, sog. Placeboeffekte, maximiert werden. Gleichzeitig sollten Noceboeffekte (z.B. die Intensivierung von Nebenwirkungen) minimiert werden (Rief, Bingel, Schedlowski, & Enck, 2011). Dabei spielen negative Behandlungserwartungen eine wichtige Rolle, die u.a. als Einstellungen gegenüber Medikamenten operationalisiert werden können und zudem direkt mit Adhärenz assoziiert sind (Foot, La Caze, Gujral, & Cottrell, 2016).

Um unspezifische Effekte in der Behandlung von Bluthochdruck zu optimieren, muss zunächst ein möglicher Placeboeffekt nachgewiesen werden. Daher wurde eine Meta-Analyse aller verfügbaren Beta-Blockerstudien mit paralleler Placebokontrollgruppe durchgeführt (23 Studien, 11.067 Patienten mit Bluthochdruck). Dabei zeigten sich robuste, blutdrucksenkende Effekte, die bereits 34% (systolisch) bzw. 47% (diastolisch) des medikamentös bedingten Blutdruckabfalls in den Beta-Blockergruppen erklärten.

In der zweiten Studie wurden Noceboeffekte mithilfe einer wahrheitsgemäßen verbalen Informationsgabe adressiert. Dabei wurden 80 gesunde Probanden in eine von zwei Informationsgruppen randomisiert: die Positivbedingung erhielt die wahrheitsgemäße Information, dass Schwindel ein Zeichen ist, dass das Medikament anschlägt. Die Kontrollbedingung erhielt die Standardinformation (Schwindel als bekannte Nebenwirkung). Nach der Einnahme von 100 mg Metoprolol bewertete die Positivbedingung auftretende spezifische Nebenwirkungen als signifikant weniger bedrohlich. Probanden, die Medikamente

eher als schädlich einstuften, unterschieden sich auch in Auftretenshäufigkeit und Intensität spezifischer Nebenwirkungen zwischen den Gruppen, zugunsten der Positivbedingung.

In der dritten Studie wurde durch eine Onlinebefragung von 273 Bluthochdruckpatienten die zentrale Rolle von Einstellungen gegenüber der verschriebenen Medikation (Notwendigkeit und Sorgen) bzgl. der Adhärenz zu Antihypertensiva in einem Strukturgleichungsmodell mit akzeptablen Fitindizes aufgezeigt. Insgesamt konnten 23% der Varianz in Adhärenz durch Einstellungen zu Medikamenten und verschiedenen Hintergrundvariablen (z.B. emotional unterstützende Arzt-Patient Kommunikation) aufgeklärt werden.

Die Ergebnisse der Dissertation zeigen, dass es für die Bluthochdruckbehandlung bedeutsam ist, erwünschte, unspezifische Effekte zu fördern und gleichzeitig personalisiert auf negative Erwartungen einzugehen. Eine Möglichkeit dazu bietet die Verbesserung der verbalen Arzt-Patient Kommunikation.

1.2 Abstract

Hypertension is highly prevalent and often requires medication to control blood pressure in order to prevent subsequent cardiovascular diseases (Kearney et al., 2005). Adherence to antihypertensive drugs, i. e., the degree to which a patient correctly follows the treatment plan, is poor and should be improved (Naderi et al., 2012). Therefore, fostering desired (unspecific) drug effects (placebo effects), while preventing nocebo effects (e.g. the aggravation of side effects) is focused (Rief et al., 2011). Negative treatment expectations can be operationalized as beliefs about medicines, which are also directly associated with drug adherence (Foot et al., 2016).

To foster unspecific effects, a robust placebo effect on blood pressure needs to be proven. Therefore, we carried out a meta-analysis of all accessible randomized controlled trials on beta-blocker therapy in patients with hypertension. Studies were supposed to have a parallel-group design including a placebo condition. In a total of 23 studies (11.067 patients), the placebo effect was robust and accounted for 34% (systolic) and 47% (diastolic) of the blood pressure lowering drug effect.

In the second study, nocebo effects were addressed via truthful verbal information. Therefore, 80 healthy participants were randomized into one of two framing groups: in the positive framing group, participants were told that dizziness was an onset sensation of a beta-blocker, while the control group received a standard information about dizziness as a common side effect. After administration of 100 mg metoprolol, participants in the positive framing group rated drug-specific side effects significantly less threatening. Subgroup analysis revealed that participants who believed that medication is harmful benefited from positive framing compared to neutral framing regarding the total number of occurrences, the intensity, and perceived threat of specific drug-attributed side effects.

In the third study, the online surveys of 273 patients with hypertension were analyzed regarding several beliefs about the specific medication in explaining variance in drug adherence. The

structural equation model was of acceptable fit and confirmed the important role of specific beliefs about medicines. The model explained 23% of variance in adherence via the necessity-concern framework and several background variables such as emotionally supportive doctor-patient communication.

The results of this thesis emphasize that fostering unspecific treatment effects while addressing negative expectations personalized are essential for the improvement of blood pressure control in hypertension. To do so, there seems to be a lot of potential in improving doctor-patient communication.

2 HINTERGRUND

2.1 Bluthochdruck

Durchschnittliche Blutdruckwerte von >140 mmHg (systolischer Blutdruck; sBP) und/oder >90 mmHg (diastolischer Blutdruck; dBP) über mindestens 24 Stunden werden in der klinischen Praxis als Bluthochdruck (Hypertonie) klassifiziert (Mancia et al., 2013). Weltweit ist ca. eine Milliarde Menschen betroffen (Kearney et al., 2005). Gerade in den unteren Bluthochdruckbereichen spüren Patienten meist keinerlei Symptome (Kjellgren, Svensson, Ahlner, & Saljö, 1997). Die Diagnose wird daher häufig bei Routineuntersuchungen gestellt. Die Kontrolle des Bluthochdrucks, also die Senkung des Blutdrucks unterhalb der Grenzwerte, ist erforderlich, um kardiovaskulären Folgeerkrankungen vorzubeugen (Chobanian et al., 2004; Sundström et al., 2015). Neben einer Empfehlung zu Lebensstilveränderungen (bzgl. Ernährung, Bewegung, Konsum von Alkohol und Nikotin etc.) werden häufig Medikamente, so genannte Antihypertensiva, zur sofortigen Kontrolle des Blutdrucks verschrieben, die auf unbestimmte Zeit einzunehmen sind (Mancia et al., 2013). Aufgrund des präventiven Charakters der Behandlung empfinden Patienten keine Erleichterung oder Linderung akuter Beschwerden. Gleichzeitig verursacht die medikamentöse Behandlung Nebenwirkungen, die sich u. a. negativ darauf auswirken können, ob Patienten die Medikamente wie vereinbart einnehmen (Vegter, De Boer, Van Dijk, Visser, & De Jong-Van Den Berg, 2013). Diese sogenannte Non-Adhärenz stellt für die Behandlung von Bluthochdruck eine große Herausforderung dar.

2.2.1 Adhärenz bei Bluthochdruckmedikamenten

Adhärenz ist gegeben, wenn Patienten sich an den gemeinsam mit dem Arzt vereinbarten Behandlungsplan halten (E. Gould & Mitty, 2010). Weichen Patienten von diesem Plan ab, z. B. indem sie die Medikation nicht oder nur teilweise einnehmen, so gelten sie als non-adhärent. In der deutschen Allgemeinbevölkerung ist in etwa jeder Dritte non-adhärent bezüglich

verschreibungspflichtiger Medikamente (Glombiewski, Nestoriuc, Rief, Glaesmer, & Braehler, 2012). Durch Non-Adhärenz entstehen neben negativen gesundheitlichen Folgen auch hohe Kosten für das Gesundheitssystem (Darkow et al., 2007). Adhärenz zu einer medikamentösen Behandlung kann sowohl objektiv durch Beobachtung der Einnahme, Auffüllraten oder durch Medikamentenspiegel im Blut, als auch subjektiv über Selbstbeobachtungsfragebögen erfasst werden (Simpson et al., 2006). Gemäß der Medicines Adherence Guidelines des National Institute for Health and Clinical Excellence (NICE; 2009) wird Non-Adhärenz in unabsichtliche und absichtliche Non-Adhärenz unterteilt. Unter unabsichtlicher Non-Adhärenz wird verstanden, dass Patienten sich zwar an den Behandlungsplan halten wollen, es aber aufgrund fehlender Ressourcen nicht können, z. B. da sie die Instruktionen zur Einnahme eines Medikaments nicht verstanden haben, Zusatzkosten nicht tragen können oder die Einnahme schlicht vergessen. Absichtliche Non-Adhärenz hingegen tritt auf, wenn die Patienten bewusst den Behandlungsplan missachten. Die Einstellungen zu Medikamenten der Patienten sind beteiligt an der Entstehung beider Unterformen von Non-Adhärenz (Horne et al., 2013).

Der Begriff Adhärenz wird häufig mit dem Begriff Compliance (Einhaltung) gleichgesetzt. Die vorliegende Arbeit verwendet den Begriff Adhärenz gemäß der Definition von E. Gould und Mitty (2010): Während Adhärenz eine transparente Patienteninformation und die gemeinsame Erarbeitung eines Behandlungsplans von Arzt und Patient voraussetzt, beschreibt Compliance das Ausmaß, in dem Patienten die vom Arzt vorgegebenen Instruktionen und Verschreibungen einhalten.

Die Adhärenz speziell in Bezug auf Bluthochdruckmedikamente ist gering (Naderi et al., 2012). Eine Hürde stellt dabei die beschriebene Symptomfreiheit von Bluthochdruck im Vergleich zum Nebenwirkungsprofil von Bluthochdruckmedikamenten dar (Vegter et al., 2013). Daraus folgen unrealistische Erwartungen der Patienten an die Behandlung, vor allem bezogen auf Symptomveränderungen und die Befürchtung von unangenehmen Nebenwirkungen, was dann in

Abwägung zu Non-Adhärenz führen kann (Marshall, Wolfe, & McKevitt, 2012). Non-Adhärenz gilt als Hauptgrund für eine unzureichende Kontrolle des Blutdrucks (Krousel-Wood, Thomas, Muntner, & Morisky, 2004; Schroeder, Fahey, & Ebrahim, 2004). Neben eines erhöhten Risikos kardiovaskulärer Folgeerkrankungen entsteht daraus häufig die Fehldiagnose einer resistenten Hypertonie (Jung et al., 2013). Das ist problematisch, da die Patienten anschließend nicht mehr die für sie optimale Behandlung erhalten.

Um die Adhärenz zu Antihypertensiva zu verbessern, wurden zahlreiche für Adhärenz günstige Faktoren identifiziert. Gut belegt sind hier positive Einstellungen gegenüber den verschriebenen Medikamenten (Foot et al., 2016). Zusätzlich können höheres Alter (Briesacher, Andrade, Fouayzi, & Chan, 2008), weibliches Geschlecht (Krousel-Wood et al., 2011), höheres Bildungsniveau und Komorbiditäten, wie z.B. Diabetes mellitus (Lowry, Dudley, Oddone, & Bosworth, 2005), günstige Kontrollerwartungen (Berglund, Lytsy, & Westerling, 2013) sowie eine zufriedenstellende Arzt-Patient-Kommunikation (Marshall et al., 2012) Adhärenz begünstigen. Einen weiteren wichtigen Faktor für Adhärenz stellen positive Behandlungserwartungen, also generelle Einstellungen gegenüber Medikamenten, dar (Horne & Weinman, 1999; siehe 2.2.4). Diese Erwartungen sind auch bei vollkommener Adhärenz der Patienten für den Symptomverlauf bedeutsam, da sie unspezifische Anteile der Medikamentenwirkung erhöhen (siehe 2.2.2) und bei der Entstehung von Nebenwirkungen beteiligt sind (siehe 2.2.3). Nebenwirkungen haben zudem einen Einfluss auf die Adhärenz zur Bluthochdruckmedikation (Vegter et al., 2013).

2.2.2 Placeboeffekte im kardiovaskulären System

Als Placebo bezeichnet man in der Regel eine Tablette ohne aktiven Wirkstoff (Benedetti, 2008). Der Placeboeffekt ist demnach die Symptomverbesserung nachdem ein Placebo eingenommen wurde, beispielsweise im Rahmen klinischer Prüfungen mit Placebokontrollgruppe, in der Medikamente auf ihre Wirksamkeit getestet werden (Enck, Bingel, Schedlowski, & Rief, 2013). Ein

Effekt zwischen der Medikamenten- und der Placebogruppe lässt folglich auf eine Wirkung des Medikaments schließen, die über den Placeboeffekt hinausgeht. Es wird dabei angenommen, dass sich die Wirkung eines aktiven Wirkstoffs additiv aus unspezifischen Effekten, z.B. der Symptomverbesserung nach Placeboeinnahme (Placeboeffekt), und spezifischen Effekten, also aus der pharmakologischen Wirkung (Verumeffekt), zusammensetzt (Kirsch, 2000). Dieses sog. additive Modell geht davon aus, dass die unspezifischen Effekte in Placebo- und Verumgruppe identisch sind. Diese Annahme wird zum Teil in Frage gestellt, da möglicherweise auch Interaktionseffekte aus spezifischen und unspezifischen Effekten Teil der Gesamtwirkung sind (Doering, Rief, & Petrie, 2014). Das additive Modell gilt jedoch dennoch als Standard, um die spezifische Medikamentenwirkung eines neuen Medikaments zu ermitteln. Im Umkehrschluss ermöglicht es die Schätzung des Placeboanteils an der Medikamentenwirkung (Winkler & Rief, 2015).

Der Placeboeffekt besteht aus verschiedenen Mechanismen, wie z.B. dem natürlichen Verlauf der Erkrankung, Effekten von Co-Interventionen oder statistischen Phänomenen, wie der Regression zur Mitte (Enck & Klosterhalfen, 2013). Zusätzlich enthält der Placeboeffekt die Placeboresponse (Placeboantwort), was den Anteil des Placeboeffekts bezeichnet, der nicht auf die o.g. Mechanismen zurückgeht, sondern ausschließlich von der Placeboeinnahme ausgelöst wird. Die Placeboresponse wird als eigenständiges Phänomen verstanden, das neurobiologisch und psychophysiologisch nachweisbar ist und maßgeblich von Behandlungserwartungen abhängt (Schedlowski, Enck, Rief, & Bingel, 2015). Um den Anteil der Placeboresponse am gesamten Placeboeffekt zu bestimmen, müssten Vergleichsgruppen ohne Behandlung herangezogen werden. In der Literatur findet man unterschiedliche Definitionen von Placeboeffekt und -response. Die vorliegende Arbeit folgt der oben beschriebenen Einordnung. Häufig werden die Begriffe synonym und teilweise auch entgegengesetzt verwendet (z.B. Kirsch, 2013).

Der Placeboeffekt ist in vielen verschiedenen Bereichen nachgewiesen, z. B. Schmerzanalgesie, psychische Störungen, immunologische und neuroendokrine Reaktionen (Schedlowski et al., 2015). Auch das kardiovaskuläre System ist sensitiv für Placebomechanismen (Meissner, 2011). Es zeigte sich beispielsweise ein Placeboeffekt auf den Blutdruck in intravenöser Placeboadministration (Grenfell, Briggs, & Holland, 1961). In experimentellen Designs wurde gezeigt, dass durch Placebointerventionen (z. B. verbale Instruktionen) der systolische Blutdruck gesenkt werden kann (Agras, Horne, & Taylor, 1982; Amigo, Cuesta, Fernandez, & Gonzalez, 1993). Diese Placeboreagibilität konnte zudem von Regression zur Mitte und anderen statistischen Phänomenen abgegrenzt werden, so dass grundsätzlich von einer Placeboresponse des Blutdrucks ausgegangen werden kann (Asmar, Safar, & Queneau, 2001). In einer randomisiert kontrollierten Medikamentenstudie erreichten 33% der Bluthochdruckpatienten in der Placebokontrollgruppe den systolischen und 31% den diastolischen Zielblutdruck (Preston, Materson, Reda, & Williams, 2000). Die untersuchte Stichprobe war jedoch klein und selektiv (nur männliche Probanden, nur milder bis moderater Bluthochdruck). Bezüglich der Placeboeffekte auf den diastolischen Blutdruck sowie in Bezug auf längerfristige Placeboeffekte auf den systolischen Blutdruck ist die Befundlage jedoch noch nicht eindeutig (Schedlowski et al., 2015).

2.2.3 Noceboeffekte im kardiovaskulären System

Der Noceboeffekt beschreibt ursprünglich das Phänomen von auftretenden Nebenwirkungen in Placebogruppen klinischer Studien, in denen kein aktiver Wirkstoff verabreicht wurde (Barsky, Saintfort, Rogers, & Borus, 2002). Der Noceboeffekt kann sich auch bei aktiven Substanzen zeigen, indem Nebenwirkungen auftreten, die nicht durch pharmakologische Eigenschaften des Medikaments verursacht werden (unspezifische Nebenwirkungen) oder indem spezifische Nebenwirkungen, die auf das pharmakokinetische Profil des Medikaments zurückgehen, intensiviert werden (Schedlowski et al., 2015). Der Noceboeffekt ist ein häufig auftretendes

Phänomen, wird als belastend erlebt und führt in der Folge zu erhöhten Behandlungskosten, z.B. aufgrund von Non-Adhärenz oder durch weitere Medikamente, die verschrieben werden, um die auftretenden Nebenwirkungen zu behandeln (Barsky et al., 2002).

Analog zu Placeboeffekten gelten Behandlungserwartungen oder bereits erworbene Behandlungserfahrungen als wichtige Faktoren, um die Entstehung von Noceboeffekten zu erklären (Finniss, Kaptchuk, Miller, & Benedetti, 2010). Experimentelle Studien zeigen, dass die verbale Informationsvermittlung einen entscheidenden Einfluss auf Noceboeffekte haben kann, z.B. bei Schmerzen bzw. Bewegungseinschränkungen von Patienten mit Parkinson (Benedetti et al., 2003). Auch in der medikamentösen Behandlung von Asthma zeigte sich, dass durch die Information, welche Nebenwirkungen durch das Medikament verursacht werden können, auch insgesamt mehr Nebenwirkungen auftreten (Myers, Cairns, & Singer, 1987; Wise et al., 2009). Bei Patienten mit gutartiger Prostata-Hyperplasie wurde gezeigt, dass bei Patienten, die vorab über sexuelle Nebenwirkungen (z. B. erektile Dysfunktion) informiert wurden, im Vergleich zu uninformierten Kontrollpatienten, mehr sexuelle Nebenwirkungen nach der Einnahme von Finasterid auftraten (Mondaini et al., 2007). Eine transparente Aufklärung über eine bevorstehende Behandlung und ihre Nebenwirkungen birgt daher ein ethisches Dilemma, da sie gleichzeitig mehr Nebenwirkungen verursacht. Ein weiteres Experiment mit Krebspatienten gab wahrheitsgemäße Informationen über die Nebenwirkungen von Tamofixen (Zikmund-Fisher, Fagerlin, Roberts, Derry, & Ubel, 2008). In der Kontrollgruppe wurde den Patienten die Auftretenswahrscheinlichkeit der Nebenwirkungen dargeboten, also wie viele Personen bestimmte Nebenwirkungen berichteten (nach Einnahme von Tamofixen respektive eines Placebos). In der Experimentalgruppe wurde das Risiko inkrementell dargeboten, also wie wahrscheinlich die jeweilige Nebenwirkung nach Einnahme von Tamofixen abzüglich der Wahrscheinlichkeit der Nebenwirkung nach Placeboeinnahme ist. Beide Gruppen erhielten zwar objektiv identische Informationen, die Patienten der Experimentalgruppe waren dennoch weniger

besorgt über Nebenwirkungen und hielten ein Auftreten im Durchschnitt für weniger wahrscheinlich.

Dieser Effekt stellt die klinische Forschung und Praxis vor eine ethische Herausforderung: Patienten sollen vor Beginn einer Behandlung transparent über Wirkweise, vertretbare Alternativen, alle bekannten Risiken und Nebenwirkungen, Vorteile und Unwägbarkeiten informiert werden, um eine aufgeklärte Zustimmung (Informed Consent) zur geplanten Behandlung geben zu können (Gillon, 2003). Gleichzeitig treten dadurch jedoch mehr Nebenwirkungen auf, was zu Behandlungsabbrüchen führen kann (Cohen, 2014). Zur Lösung des beschriebenen ethischen Dilemmas sind Methoden der Patienteninformation nötig, die eine wahrheitsgemäße Aufklärung gewährleisten und gleichzeitig negative Erwartungs- und somit Noceboeffekte minimieren.

Insgesamt werden jährlich deutlich weniger Studien zum Noceboeffekt publiziert als zum Placeboeffekt (Weimer, Colloca, & Enck, 2015). Dabei wurden kaum experimentelle Studien im kardiovaskulären Bereich veröffentlicht, die auftretende Nebenwirkungen in reinen Placebointerventionen untersuchen. Es gibt Hinweise, dass eine Neigung zu somatosensorischer Verstärkung die berichteten Nebenwirkungen in der Behandlung von Bluthochdruck vorhersagt (Doering, Szécsi, Bárdos, & Köteles, 2016), was auf die Beteiligung von Nocebomechanismen hindeutet.

2.2.4 Einstellungen gegenüber Medikamenten

Die Erwartungen von Patienten an eine bevorstehende oder laufende Behandlung gelten als zentraler Einflussfaktor auf den Erfolg pharmakologischer Behandlungen (Bingel et al., 2011). Positive Erwartungen sind dabei mit größeren Placeboeffekten assoziiert (Moncrieff, Wessely, & Hardy, 2004). Negative Erwartungen, beispielsweise hinsichtlich der auftretenden Nebenwirkungen oder des Ausbleibens des Behandlungserfolgs, können zu verringerter

Medikamentenwirkung oder vermehrt auftretenden Nebenwirkungen, also Noceboeffekten führen (Benedetti, Lanotte, Lopiano, & Colloca, 2007). Zudem können negative Erwartungen an die pharmakologische Behandlung bereits vor Einnahme den Behandlungserfolg einschränken, z.B. durch Non-Adhärenz (Foot et al., 2016).

Behandlungserwartungen in der Pharmakotherapie können unter anderem über die Einstellungen gegenüber Medikamenten erfasst werden (Horne, Weinman, & Hankins, 1999). Diese Einstellungen beeinflussen, wie Patienten die (bevorstehende) Einnahme bewerten und damit sowohl kurzfristige Wirkungen (Benedetti, Carlino, & Pollo, 2011) und Nebenwirkungen (bzw. Noceboeffekte) der Medikamente (Nestoriuc, Orav, Liang, Horne, & Barsky, 2010). Zudem bedingen diese Einstellungen, wie adhärent eine Langzeitmedikation eingenommen wird (Horne et al., 2013). Zu den vor der Erstverschreibung bereits bestehenden, allgemeinen Einstellungen gegenüber Medikamenten gehören beispielsweise Überzeugungen darüber, dass Medikamente generell schädlich sind (harm beliefs). Nachdem ein Medikament verschrieben wurde, werden spezifischere, auf die Medikation bezogene Einstellungen relevant: Die wahrgenommene Notwendigkeit der Behandlung und Sorgen über eine Reihe von negativen Konsequenzen beeinflussen die Entscheidung von Patienten, ob das verschriebene Medikament auch wie mit dem Arzt besprochen eingenommen wird (Horne & Weinman, 1999). Diese Abwägung wird in der englischsprachigen Literatur als Necessity-Concern Framework (NCF) bezeichnet und in der klinischen Forschung und Praxis eingesetzt, um Einstellungen gegenüber der verschriebenen Medikation zu bestimmen. Diese Einstellungen gegenüber Medikamenten werden meist mithilfe des Beliefs about Medicines Questionnaire (BMQ) erfasst (Foot et al., 2016; Horne et al., 1999).

3 DARSTELLUNG DES DISSERTATIONSVORHABENS

3.1 Relevanz und Herleitung der Fragestellung

Bluthochdruck ist eine weit verbreitete Erkrankung (Kearney et al., 2005) und wird häufig medikamentös behandelt, um den Blutdruck der Patienten dauerhaft zu reduzieren und somit kardiovaskulären Folgeerkrankungen vorzubeugen (Mancia et al., 2013). Gleichzeitig misslingt die Kontrolle des Blutdrucks bei vielen Patienten aufgrund von Non-Adhärenz (Krousel-Wood et al., 2004). Non-Adhärenz wird unter anderem bedingt durch negative Behandlungserwartungen, wie z.B. Einstellungen gegenüber Medikamenten (Horne et al., 2013). Außerdem sind auftretende Nebenwirkungen von Bluthochdruckmedikamenten entscheidend (Vegter et al., 2013), vor allem vor dem Hintergrund, dass Bluthochdruck im Vergleich zu Bluthochdruckmedikamenten kaum Symptome verursacht (Kjellgren et al., 1997).

Eine Möglichkeit, das Nebenwirkungsprofil der Bluthochdruckbehandlung zu reduzieren, könnte die Nutzung von Placebomechanismen darstellen, auf die das kardiovaskuläre System prinzipiell reagiert (Meissner, 2011). Allerdings konnten experimentelle Befunde bisher nur eine kurzzeitige Reagibilität in Bezug auf den systolischen Blutdruck nachweisen (Agras et al., 1982; Amigo et al., 1993). In einer Studie von Preston et al. (2000) erreichten ca. ein Drittel der Patienten aus der Placebogruppe bereits ihren Zielblutdruck, was auf einen stabileren Placeboeffekt hindeutet. Eine Möglichkeit, die bisher erhobenen Daten zu nutzen, stellen Meta-Analysen dar. Die bisher publizierten Meta-Analysen können die Frage nach einem robusten Placeboeffekt jedoch nur unzureichend beantworten, da sie in der Auswahl der Studien auf die Medikamentenwirkung ausgerichtet waren (Law & Wald, 2003). Um eine hohe Homogenität der Studien zu erreichen ist es sinnvoll, sich auf randomisiert kontrollierte Studien mit paralleler Placebovergleichsgruppe eines Bluthochdruckmedikaments zu konzentrieren (Enck & Klosterhalfen, 2013; Shedden-Mora, Nestoriuc, & Rief, 2011). Betablocker erscheinen hierfür gut geeignet, da sie seit über 50 Jahren eingesetzt werden (Black, Crowther, Shanks, Smith, & Dornhorst, 1964) und bereits häufig im

Vergleich mit Placebogruppen auf ihre Wirksamkeit untersucht wurden (Law, Wald, Morris, & Jordan, 2003). Studie 1 hatte somit zum Ziel, alle randomisiert kontrollierten Studien mit mindestens einer Betablocker- und einer Placebovergleichsgruppe meta-analytisch zusammenzufassen, um den Placeboeffekt auf systolischen und diastolischen Blutdruck sowie dessen Anteil an der Beta-Blockerwirkung zu bestimmen.

Neben der Maximierung von Placebomechanismen ist die Minimierung von Noceboeffekten bei der Bluthochdruckbehandlung relevant. Die für die Entstehung von Noceboeffekten beteiligten negativen Behandlungserwartungen können über verbale Instruktionen direkt adressiert werden (Finniss et al., 2010). Übermittelt man an Patienten die Information, dass bestimmte Nebenwirkungen auftreten können, werden diese häufiger berichtet (Wise et al., 2009). Vermeintlich geringe Abwandlungen verbaler Informationsvermittlung beeinflussen die auftretenden Nebenwirkungen deutlich (Zikmund-Fisher et al., 2008). Wenn Nebenwirkungen als ein Zeichen, dass das Medikament anschlägt („onset sensation"), wahrgenommen werden, können sie paradoxerweise auch positive Behandlungserwartungen fördern (Doering et al., 2014). Eine Variation der Aufklärung über Nebenwirkungen könnte demnach darin bestehen, eine häufig auftretende Nebenwirkung wahrheitsgemäß als „onset sensation" zu benennen und den Einfluss auf die Wahrnehmung und Bewertung von auftretenden, spezifischen Nebenwirkungen des Medikaments zu untersuchen. Die Machbarkeit dieser Intervention wurde in Studie 2 experimentell mit gesunden Probanden gezeigt. Dabei wurde ein Beta-Blocker verabreicht und in der Experimentalgruppe Schwindel als „onset sensation" benannt.

Die mangelnde Adhärenz bei der Einnahme von Bluthochdruckmedikamenten (Naderi et al., 2012) geht jedoch nicht ausschließlich auf die auftretenden Nebenwirkungen zurück (Horne et al., 2013). In der Literatur werden die Behandlungserwartungen i. S. von Notwendigkeit der und Sorgen über die verschriebene Medikation operationalisiert und als zentrale, evtl. mediierende Faktoren der Adhärenz eingesetzt (Foot et al., 2016). Verschiedene Studien haben in Regressionsmodellen

Faktoren untersucht, die mit Adhärenz zu Antihypertensiva assoziiert sind (Kressin, Orner, Manze, Glickman, & Berlowitz, 2010; Rajpura & Nayak, 2014; Ruppar, Dobbels, & De Geest, 2012). Dabei wurden Notwendigkeit und Sorgen bezüglich der Medikation in der Erklärung der Varianz von Adhärenz als zwei Einflussfaktoren unter vielen untersucht. Bisher existiert kein konfirmatorisches Modell für Bluthochdruck, wie es z. B. für Hypercholesterolemia von Berglund et al. (2013) aufgestellt wurde. Dort nehmen Notwendigkeit und Sorgen eine zentrale, mediierende Rolle ein. Ziel von Studie 3 war es, das für Hypercholesterolemia untersuchte Strukturgleichungsmodell auf Hypertonie zu übertragen und in einer Patientenstichprobe zu prüfen.

3.2 Zielsetzung des Dissertationsvorhabens

Aus der beschriebenen bisherigen Forschungslage leiten sich folgende Fragestellungen des Dissertationsvorhabens ab:

Studie 1: Wie groß sind die Effekte der Placebobehandlung bei Bluthochdruck? Wie groß ist der Placeboanteil an der medikamentösen Behandlung mit Betablockern bei Bluthochdruck? Ist ein Placeboeffekt sowohl in systolischem als auch diastolischen Blutdruck nachzuweisen?

Studie 2: Lässt sich die Wahrnehmung und Bewertung spezifischer Nebenwirkungen von Metoprolol durch die Beschreibung einer Nebenwirkung als „onset sensation“ vor der Einnahme verbessern? Profitieren vor allem jene Probanden, die eine negativere Einstellung über die generelle Schädlichkeit von Medikamenten haben?

Studie 3: Lässt sich das auf Notwendigkeit und Sorgen basierende Erklärungsmodell der Adhärenz von Berglund et al. (2013) auf Bluthochdruck übertragen und konfirmatorisch bestätigen?

4 ZUSAMMENFASSUNG DER STUDIEN

4.1 Studie 1: Der Effekt von Placebogruppen auf den Bluthochdruck: Eine Meta-Analyse von Beta-Blockerstudien

Wilhelm, M, Winkler, A., Rief, W., & Doering, B. K. (2016). Effect of placebo groups on blood pressure in hypertension: a meta-analysis of beta-blocker trials. *Journal of the American Society of Hypertension, 10(12)*, 917–929. doi: 10.1016/j.jash.2016.10.009

Hintergrund: Bluthochdruck stellt ein bedeutsames Problem des Gesundheitssystems dar (Kearney et al., 2005), da bei dauerhaftem Bluthochdruck schwere kardiovaskuläre Folgeerkrankungen entstehen können (Law & Wald, 2003). Daher werden häufig blutdrucksenkende Mittel verschrieben, u.a. Beta-Blocker, die seit den 1960er Jahren eingesetzt werden (Ezzati et al., 2005; London, Asmar, O'Rourke, & Safar, 2004). In randomisiert kontrollierten Medikamentenstudien werden häufig Placebokontrollgruppen genutzt, um die Medikamentenwirkung abzüglich des Placeboeffekts zu bestimmen. Placeboeffekte im kardiovaskulären System treten kurzfristig in experimentellen Designs und in Bezug auf den systolischen Blutdruck auf (Agras et al., 1982; Meissner & Ziep, 2011). Zur Kontrolle des Blutdrucks sind dauerhafte Effekte notwendig. Um langfristige Placeboeffekte in diastolischem und systolischem Blutdruck nachzuweisen, wurde eine Meta-Analyse randomisiert kontrollierter Beta-Blockerstudien mit parallelen Placebogruppen durchgeführt.

Methode: Die Literatur wurde umfassend via PubMed, PsycINFO, PSYNDEX, PQDT OPEN, OpenGREY, ISI Web of Knowledge und der WHO International Clinical Trials Registry Platform durchsucht. Die Effektstärken (Hedges' *g*) wurde nach dem Modell zufälliger Effekte bestimmt. Insgesamt wurden 23 Studien mit insgesamt 11.067 Patienten eingeschlossen und prä-post Effektstärken des diastolischen und systolischen Blutdrucks bestimmt und zwischen

Medikamenten- und Placebogruppen verglichen. Zusätzlich wurden einige Variablen hinsichtlich eines Moderatoreinflusses auf den Placeboeffekt untersucht.

Ergebnisse: In den Placebogruppen wurde sowohl der systolische (-0.27, p <.001) als auch der diastolische (-0.49, p <.001) Blutdruck signifikant gesenkt. Dieser Effekt macht 34% (systolisch) bzw. 47% (diastolisch) der Medikamentenwirkung aus. Moderatoreffekte zeigten, dass eine höhere Qualität der Studie und eine höhere Anzahl von vorgesehenen Terminen im Studienzentrum mit einer höheren Placebowirkung einhergingen.

Diskussion: Die Ergebnisse sprechen für einen robusten Placeboeffekt auf diastolischen und systolischen Blutdruck. Placebomechanismen sollten dringend in der Bluthochdruckbehandlung genutzt werden, beispielsweise in Form von placebokontrollierter Dosisreduktion und damit u.a. zur Senkung von Nebenwirkungen. Ein mögliches Ziel könnte dabei gesteigerte Adhärenz bei der medikamentösen Behandlung von Bluthochdruck sein.

4.2 Studie 2: Alles nur Schwindel? Ein Experiment zur Veränderung der Nebenwirkungserwartungen bei Metoprolol

Wilhelm, M, Rief, W., & Doering, B. K. (submitted). Decreasing the burden of side effects: An experimental approach with metoprolol. Manuscript submitted for publication in *International Journal of Behavioral Medicine*

Hintergrund: Patienten müssen aus ethischen Gesichtspunkten vor Ansetzung einer medikamentösen Behandlung umfassend über auftretende Nebenwirkungen informiert werden (Gillon, 2003). Gleichzeitig führt eine solche Aufklärung zu mehr Symptomen bzw. einer höheren Intensität der auftretenden Symptome (vgl. Noceboeffekt; Barsky, Saintfort, Rogers, & Borus, 2002; Schedlowski, Enck, Rief, & Bingel, 2015). Ziel dieser Studie war es, eine übliche Nebenwirkung als Zeichen, dass das Medikament anschlägt, zu benennen und dadurch die Wahrnehmung und Bewertung von Nebenwirkungen durch das anschließend verabreichte

Medikament zu verbessern. Diese Form der Informationsvermittlung könnte besonders für Patienten mit negativen Einstellungen gegenüber Medikamenten wirksam sein (Heisig, Shedden-Mora, Hidalgo, & Nestoriuc, 2015).

Methode: Gesunde, männliche Probanden (n=80) wurden in eine von zwei Informationsbedingungen randomisiert. Die positive Informationsbedingung erhielt die Information, Schwindel sei ein Zeichen, dass der Beta-Blocker (Metoprolol) jetzt wirke. Die neutrale Informationsbedingung wurde darüber informiert, dass Schwindel zwar unangenehm, jedoch bereits bekannt sei. Anschließend wurden 100 mg Metoprolol verabreicht und die auftretenden Nebenwirkungen mit der Generic Assessment of Side Effects Scale (GASE) erhoben. Zusätzlich wurde eine Subgruppenanalyse hinsichtlich der Probanden mit vorausgehenden negativen Überzeugungen hinsichtlich der Schädlichkeit von Medikamenten durchgeführt.

Ergebnisse: Auf das Medikament attribuierte, metoprololspezifische Nebenwirkungen wurden in der Positivbedingung signifikant weniger bedrohlich eingeschätzt. Die Effektgröße (Cohen's *d*) zwischen den Gruppen war klein (*d*=0.38, *p*=.049). Die Subgruppenanalyse zeigte, dass Probanden, die Medikamente generell eher für schädlich halten, sich deutlich zwischen den Gruppen unterscheiden: Es traten in der Positivbedingung weniger metoprololspezifische Nebenwirkungen auf (*d*=0.71, *p*=.009). Diese unterschieden sich zudem in Intensität (*d*=0.61, *p*=.034) und Bedrohlichkeit (*d*=0.59, *p*=.021) zwischen den Bedingungen, zugunsten der Positivbedingung.

Diskussion: Die Information zu Schwindel als Zeichen, dass das Medikament wirkt, führte zu einer veränderten Bewertung von Nebenwirkungen, vor allem bei Probanden, die Medikamente als schädlich wahrnehmen. Die Informationsgabe beim Ansetzen von Medikamenten sollte daher möglichst personalisiert werden, um die Belastung durch Nebenwirkungen dauerhaft senken zu können.

4.3 Studie 3: Alles eine Frage der Notwendigkeit und Sorgen: Ein Strukturgleichungsmodell der Adhärenz zu Bluthochdruckmedikation

Wilhelm, M, Rief, W., & Doering, B. K. (submitted). It's all a matter of necessity and concern: Explaining adherence in hypertension. Manuscript submitted for publication in *Health Psychology*

Hintergrund: Bluthochdruck wird häufig medikamentös behandelt, die Adhärenz gegenüber Bluthochdruckmedikamenten ist allerdings gering, d. h. diese werden selten so eingenommen, wie mit dem Arzt vereinbart (Naderi et al., 2012). Eine wichtige Rolle dabei scheinen Einstellungen gegenüber Medikamenten zu spielen, vor allem die wahrgenommene Notwendigkeit (Necessity) und die Sorgen (Concern) bezüglich der Bluthochdruckmedikation (Foot et al., 2016). Ziel der Studie war es, diese Überlegungen in einem theoriegeleiteten Modells abzubilden und zu prüfen.

Methode: Es wurden 273 Bluthochdruckpatienten online befragt. Einschlusskriterium war, dass bereits mindestens ein Antihypertensivum verschrieben wurde, unabhängig davon, ob sie dieses noch einnehmen. Dabei wurden Daten zu demographischen Charakteristika, gesundheits- und behandlungsrelevanten Faktoren und Kontrollerwartungen erhoben. Diese Hintergrundvariablen wurden dann mithilfe eines Strukturgleichungsmodells in Beziehung zu Notwendigkeit und Sorgen hinsichtlich der verschriebenen Medikamente und der darauf bezogenen Adhärenz gesetzt.

Ergebnisse: Die wahrgenommene Notwendigkeit der Bluthochdruckmedikation war signifikant positiv (β = .26, p = .009) und Sorgen bzgl. der Medikation signifikant negativ (β = -.51, p = .020) mit Adhärenz assoziiert. Keine der Hintergrundvariablen wies einen direkten signifikanten Pfad zu Adhärenz auf, jedoch standen einige dieser Variablen mit den Einstellungen gegenüber der Bluthochdruckmedikation in Verbindung: Die wahrgenommene Notwendigkeit der Antihypertensiva war bei Patienten mit Komorbidität erhöht (β = -.36, p < .001). Gleichzeitig stieg sie mit höherer Behandlungsdauer (β = .19, p = .004), einer guten Passung der emotional unterstützenden Arzt-Patient Kommunikation mit den Vorstellungen der Patienten (β = .12, p =

.045), höherer Intensität von Nebenwirkungen (β = .16, p = .013), der Wahrnehmung wenig persönlicher Kontrolle über die Erkrankung (β = -.13, p = .022) und erhöhter Kontrolle über die Erkrankung durch die Behandlung (β = .29, p < .001). Sorgen über die Bluthochdruckmedikation ging mit intensiveren Nebenwirkungen (β = .38, p < .001) und der Überzeugung, dass Medikamente generell eher schädlich sind, einher (β = .61, p < .001). Das Modell wies einen akzeptablen Fit auf (RMSEA = 0.61) und erklärt ca. 23% der Varianz in Adhärenz.

Diskussion: Die Notwendigkeit von und die Sorgen bezüglich der verschriebenen Bluthochdruckmedikation konnten als signifikante, zentrale Faktoren im Zusammenhang mit Adhärenz bestätigt werden. Eine personalisierte, auf die Bedürfnisse der Patienten abgestimmte Arzt-Patient Kommunikation scheint eine vielversprechende Möglichkeit zu sein, direkt die wahrgenommene Notwendigkeit der Medikation zu erhöhen und somit die Adhärenz langfristig zu steigern. Neben den Einstellungen zu Medikamenten können die beschriebenen Variablen Ärzten anzeigen, ob ein Patient ein erhöhtes Risiko für Non-Adhärenz aufweist (z.B. keine Komorbiditäten, geringe Behandlungsdauer).

5 ZUSAMMENFASSENDE DISKUSSION UND AUSBLICK

Im Rahmen der vorliegenden Dissertation ist es gelungen, einen robusten, blutdrucksenkenden Placeboeffekt nachzuweisen, die Bewertung von Nebenwirkungen eines Beta-Blockers über verbale Informationsgabe zu verändern sowie ein auf die Einstellungen zu Medikamenten konzentriertes Adhärenzmodell auf Hypertonie zu übertragen und zu bestätigen.

In Studie 1 konnte meta-analytisch der in Beta-Blockerstudien aufgetretene Placeboeffekt aggregiert werden. Dabei wurde deutlich, dass auch in den Placebogruppen der Blutdruck dauerhaft gesenkt wurde. Die Effektgrößen waren dabei zwar als klein einzuordnen, jedoch machte der robuste Placeboeffekt bereits 34% (systolisch) und 47% (diastolisch) der Medikamentenwirkung auf den Blutdruck aus.

In Studie 2 wurden die Erwartungen hinsichtlich Nebenwirkungen bei gesunden Probanden vor einmaliger Gabe eines Beta-Blockers (Metoprolol) manipuliert. Die Experimentalgruppe, für die Schwindel als Zeichen, dass das Medikament anschlägt, benannt wurde, schätzte metoprololspezifische Nebenwirkungen als weniger bedrohlich ein als die Kontrollbedingung, in der Schwindel als bereits bekannte Nebenwirkung bezeichnet wurde. Besonders deutlich wurde der Effekt zwischen Experimental- und Kontrollgruppe in der Subgruppenanalyse jener Probanden, die Medikamente generell schädlich einschätzten. Hier wurden in der Experimentalgruppe insgesamt weniger metoprololspezifische Nebenwirkungen berichtet und die berichteten Nebenwirkungen hatten im Durchschnitt eine geringere Intensität. Die Ergebnisse sprechen für die Wirksamkeit der verbalen Informationsvermittlung, die eine transparente Aufklärung der Patienten ohne Täuschung ermöglicht.

In Studie 3 konnte das untersuchte Adhärenzmodell bestätigt werden. Neben akzeptablen Modellfitindizes wurden 23% der Varianz in Adhärenz aufgeklärt. Die vermutete zentrale Rolle von Notwendigkeit und Sorgen bezüglich der Bluthochdruckmedikation wurde im Modell deutlich, da nur diese beiden Variablen einen direkten, signifikanten Effekt auf die Adhärenz hatten, nicht

jedoch die beschriebenen Hintergrundvariablen. Dabei wurde erstmals eine präzisere Operationalisierung der emotional unterstützenden Arzt-Patient-Kommunikation eingebunden, die sich als bedeutsamer Einflussfaktor auf die wahrgenommene Notwendigkeit erwies. Diese scheint einen möglichen Ansatzpunkt zu bieten, die Adhärenz bei Bluthochdruckmedikamenten zu verbessern.

5.1 Einschränkungen

Bei der Interpretation der Ergebnisse sind einige Einschränkungen zu berücksichtigen. Studie 1 beschreibt den in Beta-Blockerstudien aufgetretenen Placeboeffekt. Damit enthält der Effekt auch weitere, unspezifische Effekte neben der Placeboresponse, wie z. B. den natürlichen Symptomverlauf oder Regression zur Mitte. Zur genaueren Bestimmung der Placeboresponse hätten die untersuchten Primärstudien Wartekontrollgruppen einschließen müssen, was in keiner der analysierten Studien der Fall war. Asmar und Kollegen (2001) konnten experimentell und unter Berücksichtigung von u. a. ambulatorischen Blutdruckmessungen nachweisen, dass sich die Placeboresponse reliabel von Regression zur Mitte abgrenzen lässt. Auch hier zeigte sich eine kleine bis mittlere Effektstärke, so dass davon ausgegangen werden kann, dass es sich bei dem gefundenen Effekt v.a. um eine Placeboresponse handelt. Weiterhin schloss nur eine Primärstudie ambulatorischen Blutdruck ein (Weber et al., 2006), die Ergebnisse der Meta-Analyse stützen sich daher fast ausschließlich auf den in Kliniken gemessenen Blutdruck. Auch wenn so argumentiert werden kann, dass der Placeboeffekt auf den Blutdruck von der Messmethode unabhängig ist (Asmar et al., 2001), wurde in älteren Studien vermutet, dass Placeboeffekte in ambulatorischen 24-Stunden Assessments nicht evident sind (B. A. Gould, Mann, Davies, Altman, & Raftery, 1981; Mancia et al., 1995). Eine mögliche Erklärung besteht in der sogenannten “White Coat Hypertension” (Weißkittelhypertonie), die einen erhöhten Blutdruck bei der Messung durch einen Arzt beschreibt (Pickering et al., 1988). Andere Autoren finden keinen Effekt zwischen ambulatorischem und in der Klinik gemessenem Blutdruck (Parati, Ulian, Santucciu, Omboni, &

Mancia, 1998). Die in Studie 1 durchgeführte Moderatoranalyse unter Berücksichtigung der Anzahl der Besuche im Studienzentrum zeigte keine Hinweise auf Habituation, also die schrittweise Gewöhnung an die Situation der Messung in Bezug auf den systolischen, aber einen möglichen Effekt auf den diastolischen Blutdruck. Das bedeutet, dass der Placeboeffekt auf den diastolischen Blutdruck in den Studien mit einer höheren Anzahl an Messungen höher war. Ein Teil des Placeboeffekts könnte also auf Habituation zurückgehen. Die Bestimmung des Anteils des Placeboeffekts an der Medikamentenwirkung stützt sich auf das additive Modell (Kirsch, 2000), das seit kurzem angezweifelt wird (Enck & Klosterhalfen, 2013). Neuere Studien gehen von einer Interaktion spezifischer und unspezifischer Effekte aus, wenn ein aktives Medikament verabreicht wird (Bingel et al., 2011; Rief et al., 2016). Nimmt man ein solches Zusammenspiel der Effekte an, wäre die Höhe des Placeboeffekts in Studie 1 unterschätzt worden, da der Interaktionseffekt der Medikamentenwirkung zugeschrieben wird und diese damit im Vergleich überschätzt worden wäre. Ähnliches lässt sich hinsichtlich des Publikations-Bias feststellen: Es konnten keine unpublizierten Studien gefunden und analysiert werden, was einen Publikations-Bias wahrscheinlich macht (Easterbrook, Gopalan, Berlin, & Matthews, 1991). Üblicherweise beschreibt der Publikations-Bias die Überschätzung des meta-analytisch bestimmten Effekts dadurch, dass nur publizierte Studien mit (vermutlich) höheren Effektstärken analysiert werden, während Studien mit nicht signifikanten Effektstärken häufiger nicht publiziert werden und daher nicht in die Meta-Analyse einbezogen werden können. In Studie 1 wurden jedoch Placeboeffekte untersucht, so dass der Publikations-Bias eher zu einer Unterschätzung des aggregierten Effekts geführt haben könnte, da Medikamentenstudien mit hohem Placeboeffekt eher unveröffentlicht bleiben. Diese Vermutung legt auch die durchgeführte Trim-and-Fill-Analyse nahe.

Studie 2 wurde an gesunden Probanden durchgeführt, was zu abweichenden Erwartungen bei der Einnahme von Metoprolol geführt haben könnte, da sich gesunde Probanden vom Medikament keine Symptomverbesserung erhoffen. In der Behandlung von Bluthochdruck ist die

Erstverschreibungssituation jedoch ähnlich, da Bluthochdruck wie beschrieben kaum bis keine Symptome verursacht und Patienten keine Erleichterung oder Verminderung von Beschwerden erfahren, wenn sie Antihypertensiva einnehmen. Weiterhin wurden nur männliche Probanden untersucht, um einen möglichen Geschlechtereffekt von Blutdruckverlauf und -kontrolle zu eliminieren (Maranon & Reckelhoff, 2013). Männer haben ein erhöhtes Risiko kardiovaskulärer Erkrankungen (Reckelhoff, 2001). Zudem wurden insgesamt eher wenige, auf die Medikation attribuierte Nebenwirkungen berichtet, was zu einem Bodeneffekt geführt haben könnte. Die Stichprobengröße der Subgruppenanalyse (n=45) war eher gering und die beiden Instruktionsgruppen leicht unterschiedlich in ihrer Gruppengröße, was die Teststärke reduziert haben könnte. Allerdings wurden Tests auf Varianzhomogenität eingesetzt und die Freiheitsgrade angepasst, wenn sie nicht gegeben war.

Studie 3 basiert auf einer querschnittlichen Erhebung. Die gefundenen Zusammenhänge können daher nicht kausal interpretiert werden. Die Daten wurden zudem online und ausschließlich über Selbstauskünfte erhoben, was eine Über- oder Unterschätzung der Adhärenz ermöglicht. Während es Hinweise gibt, dass der Zusammenhang von Sorgen und Adhärenz durch subjektive Maße der Adhärenz überschätzt wird, unterscheidet sich der Zusammenhang von Notwendigkeit und Adhärenz zwischen objektiv und subjektiv erhobener Adhärenz nicht (Horne et al., 2013). Allerdings konnte objektiv nicht verifiziert werden, ob tatsächlich eine Bluthochdruckdiagnose vorlag. Das Antwortverhalten bei zum Teil sehr spezifischen Fragen wurde daher genau auf unplausible Antwortmuster geprüft, in der endgültigen Stichprobe (n=271) fanden sich darauf keine Hinweise.

5.2 Perspektiven für Forschung und Praxis

Die vorliegende Arbeit bietet einige Ansatzpunkte für weiterführende Forschung. Zunächst wäre es wünschenswert, wenn zukünftige klinische Prüfungen von Medikamenten bei Bluthochdruck neben der Medikamentengruppe(n) und der Placebokontrollgruppe zusätzlich

Wartekontrollgruppen beinhalten würden. Nur so kann die Placeboresponse vom Placeboeffekt (inkl. natürlicher Verlauf, Regression zur Mitte) abgegrenzt werden. Eine weitere Forschungsimplikation besteht in der Nutzung von Placebomechanismen in der Behandlung von Bluthochdruck. Eine vielversprechende Methode hierfür könnte die placebokontrollierte Dosisreduktion darstellen (Doering & Rief, 2012). Dabei wird vorausgesetzt, dass die Medikamentenwirkung über assoziatives Lernen konditionierbar ist. Der unkonditionierte Stimulus (UCS; hier die pharmakologischen Eigenschaften eines Antihypertensivums), führt zu einer unkonditionierten Reaktion (UCR; hier die Blutdrucksenkung). Durch die Paarung des UCS mit einem neutralen Stimulus (z.B. die Verabreichung eines Antihypertensivums in einer auffällig gefärbten Kapsel) wird der neutrale Stimulus zu einem konditionierten Stimulus (CS). In der Evokationsphase kann dieser dann ohne Zugabe eines aktiven Wirkstoffs ausreichen, um eine konditionierte Reaktion (CR) auszulösen, in diesem Fall eine Blutdrucksenkung. Bisherige Studien zeigten, dass die Therapieziele weiterhin erreicht werden, wenn Placebos mit eigentlich subtherapeutischen Dosen kombiniert werden (Ader et al., 2010; Sandler, Glesne, & Bodfish, 2010). Die Machbarkeit von placebokontrollierter Dosisreduktion bei Bluthochdruck nachzuweisen ist eine bedeutsame Implikation für die klinische Forschung.

Da Placebomechanismen den unspezifischen Anteil der Medikamentenwirkung maßgeblich beeinflussen und von Behandlungserwartungen abhängen (Bingel et al., 2011), könnte eine Verbesserung der Behandlungserwartung auch mit einer Verbesserung der Medikamentenwirkung einhergehen. Eine Möglichkeit, positive Behandlungserwartungen zu fördern, wurde in Studie 2 vorgestellt. Die mithilfe der Positivinstruktion erreichte Umbewertung von spezifischen Nebenwirkungen spricht für eine verbesserte Erwartungshaltung. Nebenwirkungen unterliegen maßgeblich Konditionierungsprozessen, ähnlich wie die erwünschte Zielwirkung des Medikaments (Rheker, Winkler, Doering, & Rief, 2016). Daher wäre eine Überprüfung des in Studie 2 gefundenen Effekts im Längsschnitt und mit Bluthochdruckpatienten bedeutsam, um eine

langfristige Umbewertung der Nebenwirkungen und dadurch ein nachhaltiges, verringertes Auftreten von Nebenwirkungen zu erreichen. Da neben Erwartungen bezüglich Nebenwirkungen auch andere Behandlungserwartungen, wie z. B. Notwendigkeit und Sorgen bezüglich der Behandlung sowie die Arzt-Patient Kommunikation wichtige Faktoren in der Erklärung von Non-Adhärenz sind (Studie 3), wäre eine Längsschnittstudie mit verschiedenen Informationsbedingungen eine logische Konsequenz der vorliegenden Dissertation. So könnte die Wirksamkeit der vorgestellten positiven Informationsgabe auch in ihren Auswirkungen auf Einstellungen zur verschriebenen Medikation bewertet werden. Zudem könnten subjektive (Selbstbericht) und objektive Maße (z.B. Auffüllraten) der Adhärenz in der Studie eingesetzt werden, um eine mögliche verzerrte Wahrnehmung der Adhärenz aufzudecken. Weiterhin könnten die in Studie 3 identifizierten Faktoren der Adhärenz (z.B. vorhandene Komorbidität, erst kürzlich begonnene Behandlung) i. S. von Risikogruppen mit in die Analyse einbezogen werden. Wie die Subgruppenanalyse in Studie 2 zeigte, reagieren Probanden mit negativen Behandlungserwartungen gegenüber Medikamenten im Allgemeinen möglicherweise deutlicher auf die Information, dass eine Nebenwirkung Zeichen für den Wirkeintritt des Medikaments ist, als die Gesamtstichprobe. Auch die Passung der emotional-unterstützenden Arzt-Patient Kommunikation könnte hier als möglicher Faktor untersucht werden.

Auch für die klinische Praxis ergeben sich Implikationen. Die Erwähnung einer spezifischen Nebenwirkung als Zeichen, dass das Medikament anschlägt, bietet einen vielversprechenden Lösungsansatz für das beschriebene Dilemma zwischen Noceboeffekt und aufgeklärter Zustimmung zu einer Behandlung. Neben dieser Intervention könnten Ärzte bei der Verschreibung neuer Medikamente die Behandlungserwartungen der Patienten erfragen oder mithilfe von Fragebögen (z. B. BMQ) schnell und präzise erfassen, um sich bei den Gesprächen besonders auf jene Patienten mit negativen Behandlungserwartungen zu konzentrieren. Zudem könnten Ärzte die Ergebnisse aus Studie 3 nutzen, um Risikogruppen für negative

Behandlungserwartungen zu identifizieren. Für niedrige wahrgenommene Notwendigkeit der Behandlung stellen eine vorhandene Komorbidität (z. B. Diabetes mellitus) und eine kürzere Behandlungsdauer (z. B. bei Erstverschreibung) Risikofaktoren dar. Ein möglicher Ansatzpunkt zur Verbesserung der wahrgenommenen Notwendigkeit stellt hingegen eine gute Passung emotional unterstützender Arzt-Patient Kommunikation mit den Präferenzen der jeweiligen Patienten dar.

In der Praxis sollten Behandlungserwartungen direkt adressiert werden, da sie die Bluthochdruckbehandlung beeinflussen können: Die in der medikamentösen Behandlung auftretenden unspezifischen (Placebo-)Effekte in der medikamentösen Behandlung machen in etwa die Hälfte der Blutdrucksenkung aus (Studie 1). Daher sollten diese z.B. über Erwartungsoptimierung gefördert werden. Auf der anderen Seite zeigt sich, dass negative Behandlungserwartungen über verbale Informationsgabe vor Medikamenteneinnahme veränderbar sind und dadurch Wahrnehmung und Bewertung von Nebenwirkungen verbessert werden (Studie 2). Zudem hängt die Adhärenz zur medikamentösen Behandlung und somit letztlich die Blutdruckkontrolle maßgeblich von Behandlungserwartungen ab (Studie 3).

5.3 Fazit

Die vorliegende Dissertation bestätigt die Wichtigkeit verschiedener Facetten von Behandlungserwartungen bei der medikamentösen Bluthochdruckbehandlung. Dabei wurden unterschiedliche Aspekte von Erwartungen beleuchtet: Zunächst konnte ein robuster Placeboeffekt auf den systolischen und diastolischen Blutdruck gezeigt werden, der fast die Hälfte der Medikamentenwirkung ausmachen kann. Wie viel davon jedoch die reine Placeboresponse ist, muss noch geklärt werden. Weiterhin wurde die Wirksamkeit einer Variante der Nebenwirkungsaufklärung zur Umbewertung auftretender Nebenwirkungen experimentell gezeigt, besonders unter Berücksichtigung negativer Einstellungen gegenüber Medikamenten. Diese zeigten sich auch als zentraler Faktor in der Erklärung von Non-Adhärenz von

Bluthochdruckpatienten. Aus der Dissertation folgt somit, dass in klinischer Forschung und Praxis der Einsatz von Erwartungseffekten eine wichtige Rolle einnehmen sollte: Die Förderung positiver Erwartungseffekte in der Blutdruckkontrolle scheint möglich über die Nutzung von Placebomechanismen (z.B. durch placebokontrollierte Dosisreduktion), die Senkung von Nebenwirkungen sowie die Erhöhung der Adhärenz zur Blutdruckmedikation, welche direkt über die Arzt-Patient Kommunikation adressiert werden könnte. Einstellungen zur Schädlichkeit und Notwendigkeit von Medikamenten sollten dabei dringend berücksichtigt werden.

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APPENDIX

A. Studien

A.1 Studie 1

Wilhelm, M, Winkler, A., Rief, W., & Doering, B. K. (2016). Effect of placebo groups on blood pressure in hypertension: a meta-analysis of beta-blocker trials. *Journal of the American Society of Hypertension, 10(12)*, 917–929. doi: 10.1016/j.jash.2016.10.009

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Research Article

Effect of placebo groups on blood pressure in hypertension: a meta-analysis of beta-blocker trials

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Abstract

Hypertension is often treated pharmacologically. Since there is evidence that the cardiovascular system is sensitive to placebo mechanisms, our aim was to conduct an effect size analysis of placebo groups in double-blinded randomized controlled parallel-group drug trials using beta-blockers to treat hypertensive patients. A comprehensive literature search via PubMed, PsycINFO, PSYNDEX, PQDT OPEN, OpenGREY, ISI Web of Knowledge, and the WHO International Clinical Trials Registry Platform provided the basis of our meta-analysis. Effect sizes were estimated using a random-effects model based on 23 studies covering a total of 11,067 participants. Main outcomes were systolic blood pressure (sBP) and diastolic blood pressure (dBP). Blood pressure was lowered in placebo groups with significant and robust effect sizes (Hedges' g). The estimates for sBP (-0.27, $P < .001$) and dBP (-0.49, $P < .001$) can be interpreted as small to moderate. The placebo response accounted for 34% of the drug response for sBP and 47% of the drug response for dBP. Our moderator analyses indicated that a higher study quality and more study site visits were marginally associated with a higher placebo response. In light of these strong placebo responses, placebo mechanisms need to be considered in order to improve antihypertensive treatment. J Am Soc Hypertens 2016;10(12):917–929.

Keywords: Diastolic; systolic.

Introduction

Placebo groups are important in randomized controlled drug trials to differentiate the specific effects of the drug from nonspecific symptom change. The physiological change in patients allocated to placebo groups, the so-called placebo effect,[1] includes symptom change caused by the natural course of the disease, various statistical artifacts (ie, regression to the mean, reporting biases, etc.), and the true placebo-induced change.[2] Positive treatment expectations, learning, and the doctor–patient interaction are major mechanisms driving the true placebo-induced change.[1] Randomized placebo controlled trials are used to contrast the specific medication effect with the overall placebo effect, assuming an additive model of both effects.[3] The effect in the drug group needs to be substantial in comparison to the effects in the placebo group in order to demonstrate the drug's efficacy. Research, however, demonstrates that not only statistically, but also clinically significant symptom improvement is seen in placebo groups in drug trials.[4]

But how much of the positive symptom change in the drug group can be observed in the placebo group? Research on antidepressant medication suggests that about 75% of the positive effect of the medication can also be observed in placebo groups.[5] For pain and generalized anxiety disorder, the proportion is around 50%.[6,7] These results are mostly based on subjective outcomes, such as self-reported scales. Therefore, it is important to look at diseases where the drug response can be quantified by objective outcomes. Winkler and Rief[8] conducted a

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meta-analysis and showed in insomnia patients that based on objective, polysomnographic data (combined data from EEG, ECG, etc.), over 60% of the positive effects of the drug were also achieved in placebo groups. Thus, placebo responses are more than reporting biases in self-reported scales. They do not only occur in psychiatric disorders, but are evident in various physiological systems and a broad range of disorders, for example, in respiratory functions, immune functions, motor functions, and others.[9]

The neuro-bio-behavioral mechanisms of the placebo response are currently being investigated (for review, see Schedlowski et al[10]). In placebo analgesia, the neurobiological mechanism could be traced down to the spinal cord level.[11] Less is known about the neurobiological mechanism of the cardiovascular placebo response, but reduction of β-adrenergic receptor activity in the heart and changes in coronary diameter have been discussed.[12,13] Efferents of the autonomous nervous system seem to contribute to this effect,[14] though the detailed neurobiological pathways have not yet been fully elucidated. This evidence, however, stems mostly from experimental approaches, and we know little about the placebo effects in the cardiovascular system in long-term treatments.

Hypertension is a meaningful example of a disease requiring permanent medication, since it is a major health issue worldwide.[15] Beta-blockers are a common permanent medication in hypertension that lowers blood pressure significantly.[16] Blood pressure reduction is important to decrease the morbidity and mortality of hypertension and ensuing cardiovascular diseases.[17] Beta-blockers were introduced in the 1960s and were recognized by most guidelines for the treatment of hypertension.[18,19] Even though they are not considered as first-line treatment for hypertension anymore,[20] beta-blockers are still being investigated in clinical trials.[21]

The cardiovascular system is sensitive to placebo mechanisms.[22] Experimental research suggests that placebo interventions can decrease systolic blood pressure (sBP).[23,24] In a double-blind randomized clinical trial, Grenfell et al[25] described a blood pressure-lowering effect in hypertensive patients through parenteral placebo administration. These placebo effects are different from the regression to the mean phenomenon.[26] It describes that if a variable is extreme on its first measurement, it tends to be closer to the average on its second measurement. Thus, hypertensive patients with a very high blood pressure on baseline measurement might have a lower blood pressure after placebo treatment, which could be confused with a placebo effect. Previous research, however, has already demonstrated in mild-to-moderate hypertension that the placebo response can be reliably distinguished from the regression to the mean phenomenon.[27] A randomized controlled trial showed that many hypertensive patients (31%) reach their goal blood pressure even in the placebo group.[28] However, the study included a small sample of only male hypertensive patients with mild-to-moderate hypertension.

At this point in time, there has been no meta-analysis that specifically investigated the relative effect of placebo groups compared to beta-blocker groups in hypertension. The existing meta-analyses[16] are not well suited to answer this research question. To adequately estimate placebo effects in RCTs, the characteristics of the trial design need to be considered. The number of trial arms and different drug types are hypothesized to have a substantial influence on the placebo effect.[29] Parallel-group designs are necessary, as crossover designs lead to an underestimation of the placebo effects.[9] Additionally, the effect sizes in placebo groups are highly correlated with those in the respective drug groups.[5] Therefore, we focused on beta-blockers and their respective placebo groups, in order to achieve a homogenous estimator of the placebo effect. Beta-blockers have been used for over 50 years[30] and have often been compared to placebo groups in randomized controlled trials.[31] In the light of this large amount of research data, a meta-analysis of beta-blocker trials seems to be well suited to investigate placebo responses in hypertension in a large sample. Thus, our meta-analysis focused on parallel-group designs only, considered only one type of medication and examined the effects of trial design (probability of receiving placebo) on the placebo effect.

Methods

We followed PRISMA guidelines for this meta-analysis.[32]

Search Procedure

We carried out a systematic search of published and unpublished research through online databases (PubMed, PsycINFO, PSYNDEX, Medline, PQDT OPEN, OpenGREY, and ISI Web of Knowledge) for randomized controlled trials using the following terms: (beta-blocker OR β-blocker) AND hypertens* AND placebo. Additionally, we searched the World Health Organization International Clinical Trials Registry platform to identify unpublished studies and contacted registered authors to gather unpublished data. We also conducted a manual review of reference lists of reviews and original studies that were previously identified through our database searches. The search was conducted in June 2015, last updated in October 2015.

Study Selection

We only included double-blind randomized controlled trials on beta-blocker treatment of hypertension. We excluded studies that did not have a placebo group or did not apply a parallel-group design. Crossover designs in particular are prone to conditioning and carry-over effects

and were therefore excluded.[1] We also excluded studies that did not report sufficient data for effect-size calculation (pre- and post-intervention assessment of blood pressure). The design had to include at least one beta-blocker group and one placebo group as we wanted to estimate the proportion of the drug response that was accounted for by the placebo response. No systematic concomitant medication was allowed during the course of the study. Studies that applied a placebo run-in phase before the application of treatment were included as long as they integrated a placebo group in the parallel-group design. The samples of the included studies were not allowed to overlap; hence, we excluded reanalyses of samples already included in the meta-analysis. To be included, the publications had to be written in English or German.

We did not define any restrictions for year of publication, duration of treatment, or sample size. Instead, we included these variables as moderators in the analysis to see whether they might influence the placebo response. Each study was checked by two independent researchers for potential inclusion. Disagreements were resolved through discussion.

Data Extraction

All outcome variables and potential moderators were extracted from the information given in the selected publication. sBP and diastolic blood pressure (dBP) were defined as main outcome variables. If available, we also included heart rate (HR) in the quantitative analysis. Resting or supine blood pressure values were used in cases in which the study reported more than one blood pressure value (standing, exercise, etc.). For each study, we also extracted the following data: overall sample size, sample size in beta-blocker group(s) and placebo group in order to estimate effect sizes; beta-blocker type used and dose of beta-blocker treatment in order to characterize the trials; year of publication, duration of treatment in days, dropout rate, mean age (placebo group), and proportion of females (placebo group) as possible moderators.

Validity Assessment

We only included double-blind randomized controlled trials using a parallel-group design. We rated the quality of each study on a validity scale[33] that was developed following PRISMA recommendations.[32] This scale contains 20 items to assess construct, internal, and external validity. In addition to our inclusion criteria (randomization, placebo control group, double blinding), the items considered if the study described the intervention sufficiently, mentioned baseline characteristics, or the dropout rate. Other items aimed at the data quality (eg, dropout rates $<$20%, intention-to-treat analyses). The score ranges from 0 to 20, with high scores indicating a high validity. The validity of each study was rated separately by two trained experts.

Quantitative Data Synthesis

All analyses were calculated using the software "Comprehensive Meta-Analysis, version 2."[34] We calculated Hedge's g to estimate the pre-post-effect sizes within the placebo groups and the drug groups separately for all three outcomes (sBP, dBP, and HR). Hedge's g is an adjusted version of Cohen's d that is calculated using the pooled standard deviation to correct for small sample sizes.[35] Cohen's recommendations apply, with 0.20 indicating a small effect, 0.50 a medium effect, and 0.80 a large effect.[36] Pre-post correlations are necessary to estimate pre-post-effect sizes assuming a random-effects model. In cases in which the studies did not provide the information necessary to determine pre-post correlations, we applied Rosenthal's recommendations[37] to use 0.70 as a conservative estimate.

We identified potential heterogeneity in effect sizes using the Q Test.[38] We also determined the ratio of true heterogeneity to total observed variation, I^2. I^2 is a ratio that ranges from 0% to 100%. It can be read as the proportion of the observed variance that suggests real differences in effect sizes. Higher values indicate a probable heterogeneity. Higgins et al[38] suggest that values of 25%, 50%, and 75% can be considered as low, moderate, and high, respectively. These methods are described in detail in Borenstein et al.[39]

The effect size estimates for sBP and dBP and HR values were then pooled across the studies to obtain a summary statistic for each of the three outcomes. To show how much of the drug effect is achieved in placebo groups, we converted the effect sizes to percentages, indicating the proportion of drug response accounted for by the placebo response.[3]

Sensitivity Analyses

In addition to our thorough literature search to identify published and unpublished studies, we used the following techniques to check whether the analyses were unbiased and robust.

Pre-post-effect sizes of placebo groups were displayed in a funnel plot to see if the distribution was symmetrical. The trim and fill method was used to recalculate the pooled effect sizes by cutting overrepresented studies (positive or negative) and by filling the plot with underrepresented studies to establish symmetry.[40]

Fail-safe N was computed, and results were considered to be robust if the number of studies necessary to lower the pooled effect size to a nonsignificant level exceeded $5K + 10$.[37,41]

We classified effect sizes as outliers if the estimated effect size was larger than 1.5 times the interquartile range of the average effect size.

Moderator Analyses

To identify possible confounders of effect sizes, we analyzed several variables as moderators.[42] We included the validity rating mentioned above to see whether the quality of the studies might have influenced their effect sizes. We also considered duration of treatment as a potential moderator of the placebo response, since a longer duration may be associated with a higher placebo response.[43,44] Year of publication was also considered as a moderator because techniques in estimating blood pressure or HR have improved. The placebo response may also have varied with average age, as older hypertensive subjects seem to have stronger placebo responses.[45] Based on previous research on placebo effects across varying diseases, we also considered the following variables as potential moderators that may be associated with higher placebo responses: percentage of women,[46] number of site visits,[47] and probability of placebo allocation.[29,48]

Results

Study Selection

As shown in Figure 1, we identified 1,284 articles. Additionally, we found 22 abstracts on the World Health Organization International Clinical trials registry. We then removed duplicates and scanned a total of 692 abstracts, of which 113 were selected for full text reading (see Figure 1 for reasons for exclusion). Of those 113 studies, 39 studies were removed because they used a crossover design, 35 because they did not report exact values for blood pressure, 6 because they were not randomized controlled trials, 5 because the placebo groups were medicated in some way, 3 because the examined disease was not hypertension, 3 due to the absence of a parallel placebo control group, 3 studies because they were not available and there was no contact address given, 2 that were republications, 1 because the medication group received a combination of beta-blockers and other drugs, and 1 because no beta-blockers were used. Additionally, we found eight eligible studies by manually reviewing the reference lists of relevant articles. There were no restrictions on sample size, culture, or year of publication as we wanted to obtain an overview of all placebo controlled beta-blocker trials on hypertension. In total, we included 23 studies in the quantitative analysis, with 67 treatment and placebo groups covering a total of 11,067 hypertensive patients.

Study Characteristics

The following beta-blockers were used in the selected studies (Table 1): nebivolol (12 conditions), metoprolol (seven conditions), atenolol (six conditions), bisoprolol (four conditions), carvedilol (three conditions), propranolol (three conditions), nadolol (two conditions), pafenolol (two conditions), acebutolol (one condition), celiprolol (one condition), and esmolol (one condition).

The year of publication ranged from 1975 to 2012. The mean duration of treatment was 159.87 days (standard

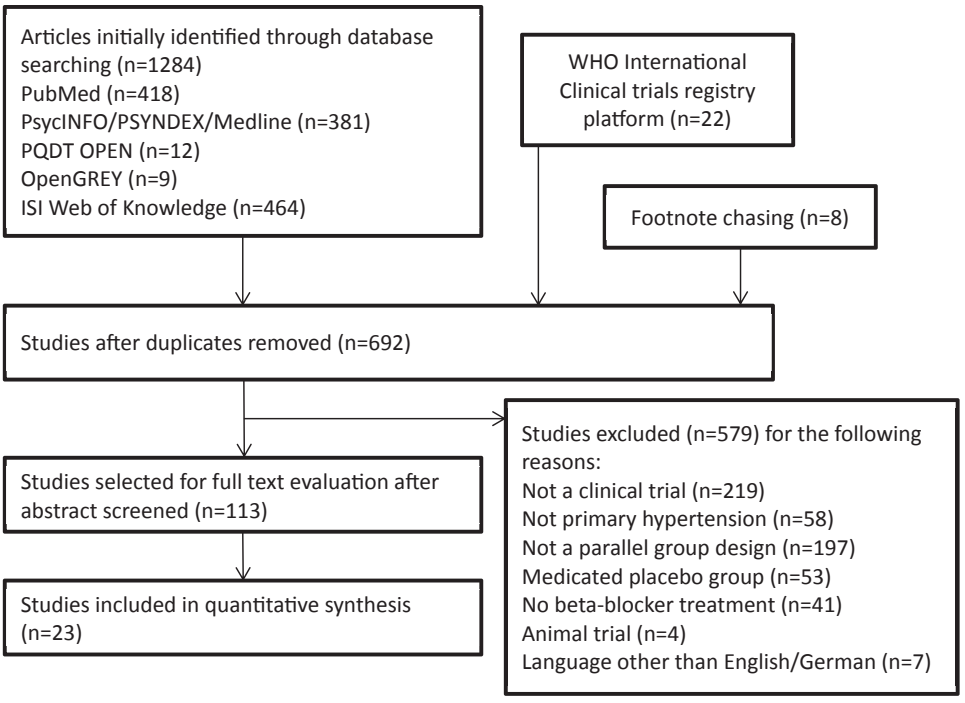

Figure 1. Flow chart of study selection. n, number of studies.

Table 1
Characteristics of included studies

Author and Year	*N* Total (βN/pN)*	Drug in Treatment Group (Dose)	Class of Drug in Treatment Group	Trial Duration in Days	Average Age in Placebo Group	% of Female Participants in Placebo Group	Outcome Variables	Quality Score
Ades et al (1990)[49]	30 (20/10)	Metoprolol (100 mg); propranolol (80 mg)	β^1-receptor blocker; nonselective β-blocker	77	48.0	30.0	sBP, dBP, HR	12
Adsett et al (1989), education[50]	24 (12/12)	Nadolol (80 mg)	Nonselective β-blocker	56	49.4	0.0	sBP, dBP	17
Adsett et al (1989) relaxation[50]	23 (11/12)	Nadolol (80 mg)	Nonselective β-blocker	56	42.5	0.0	sBP, dBP	17
Baez et al (1986)[51]	24 (12/12)	Atenolol (100 mg)	β^1-receptor blocker	98	—	33.3	sBP, dBP	13
Berglund et al (1985)[52]	31 (22/9)	Pafenolol (25 mg, 50 mg)	β-adrenergic receptor blocker	28	51.4	22.5	sBP, dBP, HR	13
Carr et al (2012)[53]	3315 (1102/2213)	Atenolol (50 mg)	β^1-receptor blocker	2117	70.3	48.0	sBP, dBP	13
Chrysant and John (1992)[54]	127 (84/43)	Atenolol (25 mg, 50 mg)	β^1-receptor blocker	28	53.0	46.5	sBP, dBP, HR	13
Davidov and Singh (1994)[55]	240 (180/60)	Bisoprolol (5 mg, 10 mg, 20 mg)	β^1-adrenergic receptor blocker	28	53.0	35.0	sBP, dBP, HR	13
Frishman et al (1995)[56]	226 (151/75)	Bisoprolol (5 mg)	β^1-adrenergic receptor blocker	28	54.0	36.0	sBP, dBP	14
Hansson et al (1975)[57]	44 (21/23)	Atenolol (200 mg)	β^1-receptor blocker	112	45.0	43.5	sBP, dBP, HR	11
Houston et al (1990)[58]	61 (30/31)	Atenolol (50 mg)	β^1-receptor blocker	112	52.0	55.0	sBP, dBP	12
Jäätelä et al (1990) elderly[59]	35 (17/18)	Metoprolol (50 mg)	β^1-receptor blocker	28	68.8	61.1	sBP, dBP, HR	14
Jäätelä et al (1990) mild[59]	62 (35/27)	Metoprolol (50 mg)	β^1-receptor blocker	28	53.0	50.0	sBP, dBP, HR	13
Krantz et al (1988)[60]	63 (24/12)	Atenolol (25 mg); propanolol (40 mg)	β^1-receptor blocker; nonselective β-blocker	28	45.2	0.0	sBP, dBP, HR	11
MHRG (1991)[61]	347 (126/221)	Acebutolol (400 mg)	Cardioselective β-blocker with intrinsic sympathomimetic activity	365	54.9	38.5	sBP, dBP, HR	16
Olkinuora et al (2006)[62]	56 (27/29)	Celiprolol (200 mg)	β^1-receptor blocker and β^2-receptor partial agonist	90	62.0	6.9	sBP, dBP	13
Papadimetriou et al (2006)[63]	480 (328/152)	Metoprolol (25 mg, 50 mg, 100 mg, 200 mg)	β^1-receptor blocker	56	53.0	45.0	sBP, dBP	16
Pérez-Stable et al (2000)[64]	291 (147/144)	Propanolol (400 mg)	Nonselective β-blocker	90	45.0	9.0	sBP, dBP, HR	17
Saunders et al (2007)[65]	300 (251/49)	Nebivolol (2.5 mg, 5 mg, 10 mg, 20 mg, 40 mg)	β^1-receptor blocker with nitric oxide-potentiating vasodilatory effect	84	49.7	53.1	sBP, dBP, HR	15
Sharma et al (1996)[66]	45 (30/15)	Esmolol (100 mg, 200 mg)	β^1-receptor blocker	0.0007	50.8	66.7	sBP, dBP, HR	14
Weber et al (2006)[67]	337 (253/84)	Carvedilol (20 mg, 40 mg, 80 mg)	Nonselective β-blocker	42	52.6	33.0	sBP, dBP	13
Weber et al (2012)[68]	283 (188/95)	Nebivolol (20 mg)	β^1-receptor blocker with nitric oxide-potentiating vasodilatory effect	42	47.4	49.5	sBP, dBP	15

(*continued*)

Table 1 (*continued*)

Author and Year	*N* Total (ßN/pN)*	Drug in Treatment Group (Dose)	Class of Drug in Treatment Group	Trial Duration in Days	Average Age in Placebo Group	% of Female Participants in Placebo Group	Outcome Variables	Quality Score
Weiss et al (2007)[69]	909 (828/81)	Nebivolol (1.25 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, 40 mg)	β^1-receptor blocker with nitric oxide-potentiating vasodilatory effect	84	56.0	43.2	sBP, dBP, HR	14

dBP, diastolic blood pressure; HR, heart rate; quality score, quality scale (range: 0–20 points); sBP, systolic blood pressure.
* Number of subjects in the ß-blocker treatment condition (ßN) and number of subjects in the control condition (pN).

deviation [SD] = 432.6, median = 56). Altogether we analyzed 3,427 patients treated with placebo and 7,640 patients treated with beta-blockers. In the placebo groups the mean age was 63.9 (SD = 9.1) years. In total, 43.9% of the patients in the placebo groups were women. The mean study quality was rated 13.9 out of 20 (SD = 1.79) and ranged from 11 to 17. We estimated the interrater reliability (Cohen's Kappa) to be $\kappa = 0.867$. Any disagreements were resolved through discussion to obtain consistent values.

Quantitative Data Synthesis

Table 2 shows the effect sizes for every placebo group and outcome. Of 23 placebo groups, 17 revealed a significant effect size in at least one blood pressure outcome. Table 3 shows I^2 values and Q-tests as a measure of heterogeneity; notably, the I^2 for sBP and dBP can both be interpreted as high.

As presented in Table 3, the pooled within-group effect sizes (Hedge's g) of the placebo groups were significant for both blood pressure outcomes (sBP and dBP), with small-to-medium effect sizes.[36] This indicates that both sBP and dBP are lowered significantly by placebo intake. No significant placebo response was found in the 13 studies in which HR after placebo intake was reported.

Proportion of Drug Response Accounted for by the Placebo Response

Table 3 shows that the placebo response accounted for 34% of the drug response for sBP and 47% for dBP. Thus, almost half of the drug response can be observed in the placebo group.

Sensitivity Analysis

Trim and fill analysis indicated that the presented results were biased, meaning that studies with higher drug-placebo differences were overrepresented. It is likely that trials with lower drug-placebo differences remain unpublished, for example trials in which blood pressure effect sizes in placebo groups might have been moderate to large. Thus, placebo effects are likely to have been underestimated.

As demonstrated in Table 3, fail-safe N analyses revealed that more than 125 nonsignificant studies would be necessary to determine the effect sizes as robust. Both blood pressure effect sizes can be considered robust as values were above 125. However, the results of fail-safe N must be interpreted with caution since the resulting estimates of additional studies seem to vary widely.[70]

In sBP, one study had to be removed from the analysis as an outlier.[53] This study showed an effect size in the placebo group larger than 1.5 times the interquartile range of the average effect size.

Table 2
Efficacy of placebo treatment for all outcomes

Author, Publication Year	Outcome Variables	Pre–Post			
		g	SE	95% CI	*P*-Value
Ades et al (1990)	sBP	−0.55*	0.24	−1.02 to −0.07	.025
	dBP	−0.63*	0.25	−1.12 to −0.14	.012
	HR	0.28	0.23	−0.17 to 0.73	.227
Adsett et al (1989) Education	sBP	−1.04**	0.34	−1.71 to −0.37	.002
	dBP	−0.96**	0.33	−1.61 to −0.31	.004
Adsett et al (1989) Relaxation	sBP	−0.65*	0.30	−1.24 to −0.06	.030
	dBP	−0.85**	0.32	−1.47 to −0.22	.008
Baez et al (1986)	sBP	−0.13	0.21	−0.54 to 0.28	.541
	dBP	−0.42	0.22	−0.85 to 0.01	.053
Berglund et al (1985)	sBP	−0.22	0.24	−0.69 to 0.24	.350
	dBP	−0.23	0.24	−0.70 to 0.23	.323
	HR	0.07	0.23	−0.39 to 0.53	.759
Carr et al (2012)	sBP	−1.46**	0.02	−1.51 to −1.42	<.001
	dBP	−0.54**	0.02	−0.58 to −0.51	<.001
Chrysant et al (1992)	sBP	−0.27*	0.12	−0.50 to −0.04	.022
	dBP	−1.09**	0.15	−1.38 to −0.80	<.001
	HR	−0.08	0.12	−0.31 to 0.15	.501
Davidov et al (1994)	sBP	−0.18	0.10	−0.38 to 0.01	.068
	dBP	−0.14	0.10	−0.34 to 0.05	.148
	HR	0.06	0.10	−0.13 to 0.26	.521
Frishman et al (1995)	sBP	−0.21*	0.09	−0.39 to −0.04	.017
	dBP	−0.43**	0.09	−0.62 to −0.25	<.001
Hansson et al (1975)	sBP	−0.14	0.16	−0.45 to 0.17	.379
	dBP	−0.43**	0.16	−0.75 to −0.11	.009
	HR	0.02	0.16	−0.29 to 0.32	.917
Houston et al (1990)	sBP	−0.27*	0.14	−0.55 to −0.00	.047
	dBP	−1.04**	0.17	−1.37 to −0.71	<.001
Jäätelä et al (1990) elderly	sBP	−0.28	0.18	−0.63 to 0.07	.116
	dBP	−0.23	0.18	−0.57 to 0.12	.200
	HR	−0.52**	0.19	−0.89 to −0.15	.005
Jäätelä et al (1990) mild	sBP	0.04	0.14	−0.24 to 0.32	.777
	dBP	−0.38*	0.15	−0.68 to −0.09	.011
	HR	0.00	0.14	−0.28 to 0.28	1.000
Krantz et al (1988)	sBP	−0.09	0.21	−0.50 to 0.32	.666
	dBP	0.08	0.21	−0.33 to 0.49	.705
	HR	−0.07	0.21	−0.48 to 0.34	.741
MHRG (1991)	sBP	−0.55**	0.06	−0.66 to −0.44	<.001
	dBP	−0.84**	0.06	−0.96 to −0.73	<.001
	HR	−0.31**	0.05	−0.42 to −0.21	<.001
Olkinuora et al (2006)	sBP	−0.35*	0.14	−0.63 to −0.07	.016
	dBP	−0.32*	0.14	−0.61 to −0.04	.024
Papadimetriou et al (2006)	sBP	−0.20*	0.08	−0.36 to −0.04	.012
	dBP	−0.51**	0.09	−0.68 to −0.35	<.001
Pérez-Stable et al (2000)	sBP	−0.41**	0.07	−0.55 to −0.28	<.001
	dBP	−0.90**	0.08	−1.05 to −0.75	<.001
	HR	−0.21**	0.06	−0.34 to −0.08	.001
Saunders et al (2007)	sBP	−0.18	0.11	−0.39 to 0.04	.109
	dBP	−0.38**	0.11	−0.60 to −0.16	.001
	HR	−0.23*	0.11	−0.45 to −0.01	.038
Sharma et al (1996)	sBP	0.12	0.19	−0.25 to 0.49	.523
	dBP	−0.05	0.19	−0.42 to 0.32	.788
	HR	0.09	0.19	−0.28 to 0.47	.620

(*continued on next page*)

Table 2 (*continued*)

Author, Publication Year	Outcome Variables	Pre–Post			
		g	SE	95% CI	*P*-Value
Weber et al (2006)	sBP	−0.07	0.08	−0.24 to 0.09	.379
	dBP	−0.18*	0.08	−0.34 to 0.01	.035
Weber et al (2012)	sBP	−0.46**	0.08	−0.63 to −0.30	<.001
	dBP	−0.67**	0.09	−0.84 to −0.50	<.001
Weiss et al (2007)	sBP	−0.30**	0.09	−0.47 to −0.12	.001
	dBP	−0.32**	0.09	−0.49 to −0.15	<.001
	HR	0.02	0.09	−0.17 to 0.20	.851

dBP, diastolic blood pressure; HR, heart rate; sBP, systolic blood pressure.
*$P < .05$; **$P < .01$.

Moderator Analysis

As presented in Table 4, no moderators that might have substantially influenced the placebo response in blood pressure were identified. The duration of treatment had a statistically significant effect, but with a regression weight too small to interpret ($\beta < -.01$, $P < .001$). Both effect sizes in blood pressure were significantly associated with study quality (sBP: $\beta = -.06$, $P = .003$; dBP: $\beta = -.07$, $P = .016$). Additionally, dBP was associated with the number of site visits ($\beta = -.07$, $P = .002$); however, all three regression weights were small. This suggests that higher study quality and more study site visits were only marginally associated with a higher (negative) effect size, indicating a higher placebo response.

Discussion

Hypertensive patients in randomized controlled beta-blocker trials respond to placebo interventions. This means that even the intake of an inert pill lowers blood pressure significantly with robust small-to-medium effect sizes. The blood pressure change was quantified through objective measures of sBP and dBP. Almost half of the blood pressure-lowering effect that was observed in the drug groups was also observed in the placebo groups. For sBP, no substantial moderators of the placebo effect were identified. For dBP, a higher number of site visits and better study quality were only weakly associated with increased placebo responses.

Our finding of a significant placebo effect in antihypertensive treatment supports the proposition that placebo effects are relevant for the cardiovascular and autonomous nervous system.[22] A blood pressure-lowering placebo effect in hypertension was first suggested by Grenfell et al.[25] They found a transient decrease of sBP and a sustained reduction of dBP after approximately 1 year of parenteral placebo administration. Accordingly, our results indicate that both blood pressure values were lowered in placebo groups, with a moderate placebo effect size on dBP and a small placebo effect size on sBP. On the contrary, experimental approaches did not show placebo effects on dBP, while successfully modulating sBP in normotensive and hypertensive participants.[14,23,24] Therefore, it was recently

Table 3
Pooled within-group effect sizes for all outcome variables for placebo and ß-blocker treatment

Outcome	k	cN	*g*	95% CI	SE	*z*	*P*	I^2	Fail-Safe N	Placebo Response (%)
Placebo treatment										
sBP	20	22	−0.27**	−0.36 to −0.18	0.04	−6.18	<.001	64.73	679	
dBP	21	23	−0.49**	−0.60 to −0.39	0.05	−9.18	<.001	84.64	3626	
HR	13	13	−0.09	−0.20 to 0.01	0.05	−1.79	.074	61.49	—	
ß-Blocker treatment										
sBP	21	44	−0.79**	−0.98 to −0.60	0.10	−8.07	<.001	97.28	22,607	34
dBP	21	44	−1.04**	−1.13 to −0.94	0.05	−20.63	<.001	87.52	34,612	47
HR	13	29	−0.74**	−0.85 to −0.63	0.06	−13.19	<.001	83.33	7160	—

CI, confidence interval; cN, number of conditions in the analysis; dBP, diastolic blood pressure (mm Hg); fail-safe N, the number of studies with a treatment effect of 0 that would be needed to lead to a nonsignificant overall result; HR, heart rate (beats/min); I^2, ratio (0 to 100%) indicating the proportion of the observed variance that reflects real differences in effect sizes (values of 25%, 50%, and 75% can be considered low, moderate, and high, respectively); k, number of studies in the analysis; placebo response, proportion of placebo effect in pre-post pharmacological effect as a percentage; sBP, systolic blood pressure (mm Hg); SE, standard error.
**$P < .01$.

Table 4
Moderator analysis for effect of placebo treatment on sBP and dBP

Moderator	cN	β	SE	*P*-Value
sBP				
Quality of study	22	−.06**	0.02	.003
Year of publication	22	<−.01	0.00	.796
Duration of treatment	22	<−.01**	0.00	.004
Mean age of sample	21	<.01	0.01	.747
% Females in study sample	22	<.01	0.00	.089
No. of site visits	22	−.02	0.01	.367
Probability of placebo allocation	22	<−.01	0.00	.824
dBP				
Quality of study	23	−.07*	0.03	.016
Year of publication	23	<.01	0.01	.813
Duration of treatment	23	<−.01	0.00	.645
Mean age of sample	22	.01	0.01	.474
% Females in study sample	23	<.01	0.00	.816
No. of site visits	23	−.07**	0.02	.002
Probability of placebo allocation	23	<−.01	0.00	.568

cN, number of conditions in the analysis; dBP, diastolic blood pressure; sBP, systolic blood pressure; SE, standard error; β, estimated slope in meta regression analyses.
*$P < .05$; **$P < .01$.

stated that cardiovascular placebo effects other than on sBP require further clarification.[10] sBP seems to be more responsive to short-term interventions. Our meta-analytic data are able to reveal long-term effects, which suggest the existence of a robust placebo effect on dBP. However, further research is needed especially regarding neuro-bio-behavioral mechanisms affecting sBP and dBP differently. On the other hand, our results confirmed a previous experimental finding that there is no placebo response in HR when blood pressure changes are the main outcome.[14] The authors suggest that specifically autonomic nervous system afferents are involved in the placebo effect on sBP control. Further research is needed to investigate this assumption and to clarify mechanisms involved in the placebo effect on dBP and HR. An HR-lowering placebo effect has been demonstrated; thus, HR can be influenced in placebo interventions. However, this was the case in pain analgesia designs, where a reduction in sympathetic activity is evident[12] and is hypothesized to be involved in anticipatory pain analgesia.[71] Such an anticipatory HR reduction, however, seems not relevant in hypertension.

There are a few limitations regarding the present analysis. The estimated placebo response in this meta-analysis also includes nonspecific effects like natural course of symptoms or regression to the mean. It would have been necessary to include waitlist control conditions in the analysis to differentiate these factors of influence. None of the studies we analyzed used a waitlist control group or a "no treatment" condition. However, Asmar et al[27] successfully demonstrated in an experimental design assessing both ambulatory and clinic blood pressure that the significant placebo-induced change in mild-to-moderate hypertension can reliably be distinguished from the regression to the mean phenomenon. Hence, we assume that our results reflect the true placebo-induced change more than other nonspecific effects (eg, regression to the mean, reporting biases).

The results of our study pertain to placebo responses in clinic blood pressure, not to the ambulatory assessed placebo response. Only one study included in the analysis used 24-hour blood pressure assessments.[67] While some studies argue that the placebo effect is independent of the method used to measure blood pressure,[27] others suggest that placebo effects in blood pressure do not occur in ambulatory assessments, eg over 24 hours.[72,73] A possible explanation could be the "white-coat hypertension" phenomenon,[74] involving a rise in blood pressure when measured by a clinician in a white coat. A fall in blood pressure during the treatment phase could just be the effect of habituation to clinician-administered examination. However, other authors argue that this phenomenon is not evident in the differences between ambulatory and onsite assessments.[75] Our moderator analysis demonstrated no evidence for habituation (ie, increased placebo effects in studies with a higher number of site visits) for sBP, but a possible effect of habituation for dBP. Independently of habituation effects that may be present in the blood pressure assessment method, however, the number of site visits has also been identified as a moderator in studies investigating placebo effects in other conditions.[47] To clarify the situation, it would be helpful to further investigate possible differences in placebo responses assessed by clinicians and through ambulatory assessment.

Our procedure to estimate the proportion of the drug response that can be observed in the placebo group relies on the additive model,[3,8] which has recently come under doubt.[9] Recent research suggests an interplay of drug effects and placebo effects (eg, expectancy) that is inherent to any application of a medication.[76] Based on this interplay, it has been suggested that there is an interaction between drug application and the context in which the drug is given.[77] If that interactive model was true, we would have underestimated the placebo response using the present method.[3] Our method to determine the relative share of the drug effect by the placebo effect by subtraction ascribes the possible effect of the interaction to the drug effect, thus overestimating the drug response and underestimating placebo responses.

We did not find any unpublished studies to include in our meta-analysis, and therefore, publication bias should be considered. Our sensitivity analyses, however, indicate the robustness of our findings.[78] Despite this, our trim and fill analyses indicated a publication bias. This would normally be inconsistent with describing our results as robust. But as

we investigated placebo groups, publication bias would lead to underestimation of the placebo effect size. Unpublished studies that would challenge our results are those studies that would demonstrate particularly low placebo effects. Studies with lower placebo effects, however, are more likely to be published, as they favor the superiority of the drug response over the placebo response. Studies with high placebo effects (and possibly no drug superiority) are more likely to remain unpublished.

The strength of our work lies in the comprehensive literature search that allows us to generalize our results across all published research on beta-blockers. The most important inclusion criterion for examined studies was a randomized and controlled trial design. This resulted in the very high quality of our analyzed studies, as no studies of poor quality were included. This impression is also supported by our quality ratings, which revealed a high study quality assessed with an ''almost perfect'' interrater reliability.[79,80] Notably, our meta-analysis is the first to quantify the proportion of the placebo response in the beta-blocker response.

Given our result that almost half of the effect of beta-blockers is also observable in placebo groups, it should be considered that the treatment of hypertension might benefit from harnessing these placebo mechanisms. Placebo mechanisms (eg, positive treatment expectations) do not only drive placebo responses but can also strengthen or weaken responses to potent medications.[76] Optimizing the treatment context to maximize placebo mechanisms could thus also improve drug effects.[1] An optimal treatment context could include building confidence in the medication by explaining its effectiveness to the patient or taking time to establish a positive patient–provider interaction. This is not yet a well-established concept in cardiovascular disease research or practice. Nevertheless, there are several opportunities to optimize the treatment expectation of the patients in order to improve treatment outcome, as already shown in cardiovascular surgery[81,82] and myocardial infarction.[83] Similarly, treatment expectations that are fostered in the patient–physician interaction could contribute to better outcomes in the pharmacotherapy of hypertension. This would not only improve the drug effect through placebo mechanisms, but also improve adherence to antihypertensive medication, which is poor.[84]

Another promising idea to reduce the patients' side effects and thereby strengthen drug adherence is placebo controlled dose reduction.[85] Placebo controlled dose reduction relies on classic conditioning and thus represents a form of associative learning. The starting point is an unconditioned stimulus (eg, pharmacological properties of a beta-blocker) that leads to an unconditioned response (eg, blood pressure reduction). By pairing the unconditioned stimulus with a neutral stimulus in the acquisition phase (eg, application of beta-blocker by distinctly colored capsule), the neutral stimulus becomes a conditioned stimulus. In the evocation phase, the capsule itself (ie, without active ingredient) then elicits a conditioned response that approximates the original unconditioned response, that is, blood pressure reduction. Recent trials of placebo controlled dose reduction indicate that therapeutic gains can be maintained if placebos are combined with subtherapeutic drug regimens.[86,87] Thus, it has the potential to reduce the amount of medication needed for the treatment and to alleviate the side effects for the patients' benefit. A crucial issue pertains to the stability of these effects which certainly warrants further research. Regarding the substantial placebo effects on both sBP and dBP, however, it may ultimately be possible to utilize placebo mechanisms in pharmacotherapy to gain satisfactory blood pressure control.

To conclude, the significant change in blood pressure in the placebo groups indicates that placebo mechanisms play an important role in blood pressure control. These mechanisms seem to affect sBP as well as dBP and could therefore be exploited in drug application to induce positive treatment expectations, reduce side effects, strengthen treatment adherence, and thus improve the treatment of hypertension.

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A.2 Studie 2

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DECREASING THE BURDEN OF SIDE EFFECTS THROUGH FRAMING: AN EXPERIMENTAL INVESTIGATION WITH METOPROLOL

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ABSTRACT

Purpose: Informing patients about side effects increases the occurrence and intensity of side effects in response to medical treatment. Since the obligatory informed consent procedure in drug treatments requires transparency, the aim was to "frame" a common side effect positively prior to drug administration, which should result in side effects rated as less threatening, and a decrease in their occurrence and intensity.

Methods: Healthy male participants (n=80) were randomized to one of two framing groups. The positive framing group was informed that the common side effect dizziness was a sign that the drug had started to work, while the neutral framing group was told that dizziness is an unpleasant but well-known side effect. After administration of 100 mg metoprolol, side effects were measured with the Generic Assessment of Side Effects Scale (GASE). A subgroup analysis considered the role of pre-existing negative beliefs about the general harm of medication.

Results: Metoprolol-specific drug-attributed side effects were rated significantly less threatening in the positive framing group. The between-group effect size (Cohen's *d*) was moderate (*d*=0.38, *p*=.049). Subgroup analysis revealed that participants who believed that medication is harmful benefited from positive framing compared to neutral framing regarding the total number of occurrences (*d*=0.71, *p*=.009), the intensity (*d*=0.61, *p*=.034), and perceived threat (*d*=0.59, *p*=.021) of specific drug-attributed side effects.

Conclusions: The framing was efficient in decreasing specific side effect measures, particularly in participants with a tendency to believe that medicine is harmful. Informed consent procedures should therefore be personalized, focusing on patients with negative treatment beliefs.

Keywords: side effects; nocebo; informed consent; framing; experiment.

Word count: 3998

BACKGROUND

The nocebo effect describes the phenomenon of side effects occurring in placebo groups of clinical trials, i.e. when no active drug treatment is administered [1]. The nocebo effect can also occur in active drug groups by causing side effects that are not explained by the pharmacological properties of the drug (hence non-specific) or by aggravating specific side effects that match the pharmacokinetic profile of the drug [2]. The nocebo effect is common, distressing to patients, and may lead to rising treatment costs due to non-adherence or the prescription of additional medication to treat these side effects [1]. A contributing mechanism is assumed to be treatment expectations, which are influenced by verbal suggestions or treatment experience [3]. Verbal suggestions have been shown to mediate nocebo effects, e.g. in pain or motor performance [4]. This means that receiving more information about potential side effects results in more reported side effects, e.g. headaches in asthma patients treated with a leukotriene receptor antagonist [5].

This draws attention to informed consent procedures, which must convey information regarding the nature of the medical treatment, reasonable alternatives to the proposed intervention and relevant risks, benefits, and uncertainties related to each alternative. Transparency, respect to the person and thus informed consent are essential for medical ethics [6]. Simultaneously, as mentioned above, informing about side effects also appears to have negative effects: patients who were enrolled in a trial for the treatment of unstable angina experienced minor gastrointestinal side effects significantly more often when these side effects were outlined in the informed consent procedure. These patients also withdrew from the study more often due to the mentioned side effects [7]. A more recent experimental approach in benign prostatic hyperplasia showed that patients who received information about the occurrence of sexual side effects due to finasteride treatment reported significantly more sexual side effects than the control group, which was not informed about these side effects [8]. A

similar approach demonstrated more frequent reports of erectile dysfunction in patients treated with beta-blockers after they were informed about potentially occurring side effects of erectile functions [9]. This research points to an ethical conundrum: patients need to be informed about side effects to make informed choices. However, informing the patient about side effects may increase the occurrence and intensity of side effects and thus harm the patient.

In order to address this issue, different approaches of presenting truthful treatment information, i.e. the framing of treatment information such as occurrence of side effects, have been the focus of recent studies, e.g. in cancer research [10]. An experiment with cancer patients presented truthful information about the side effects of tamoxifen [11]. In the control group, the informed consent presented the total risk of side effects, i.e. how many people reported a certain side effect after taking either no medication (placebo) or tamoxifen. In the experimental group, the risk of tamoxifen side effects was presented as incremental, i.e. the percentage of people reporting the respective side effects after tamoxifen treatment, after subtracting the placebo-induced rate of the side effect. Patients in the experimental group (incremental risk) were less worried about adverse side effects and assumed a smaller likelihood of side effect occurrence, although the information was objectively the same. O'Connor, Pennie, and Dales [12] showed that influenza immunization caused fewer side effects if the informed consent described the percentage of individuals who remain free of influenza and free of side effects with vaccination. In the control group, the participants were informed about the same probability, but it was framed as the percentage of individuals who will experience side effects and acquire influenza despite vaccination. These findings showed that the occurrence and intensity of drug-specific side effects can be changed by verbal suggestion without deceiving the patients and thus adhering to the rules of informed consent.

While this line of research tries to minimize the occurrence of both non-specific (nocebo) side effects and specific, drug-induced side effects, another line of research indicates

that side effects may sometimes have paradoxically positive effects for the patient's treatment expectations. In clinical trials that compare drug and placebo effects, minor bodily symptoms (i.e. onset sensations of the drug) can unblind trial participants [13]. If side effects are attributed to drug intake, they may convince participants that they have received the real drug and thus foster positive treatment expectations [14]. This hypothesis was tested empirically in the domain of placebo analgesia in healthy volunteers using both inert placebos and active placebos that mimic the real drug's side effects [15]. In inert placebo conditions, the well-known expectancy effect of placebo analgesia was replicated: participants who believed they had received an active drug reported the highest pain thresholds. Compared to participants who noted no bodily symptoms after "medication" intake, participants with minor onset sensations from active placebo intake demonstrated a greater placebo effect. This may also apply to clinical practice: the appraisal of the first experienced side effects, i.e. the onset sensations of the drug, might determine whether the patients will be able to establish a positive treatment expectation.

Therefore, it makes sense to combine the findings from these two lines of research. In the context of the obligatory informed consent, it should be possible to positively frame benign drug-induced side effects as onset sensations and thus improve treatment expectations. A possible solution could be to describe them as what they are: sensations that indicate the onset of the beneficial drug effect. Since nocebo research suggests that the informed consent of a drug leads to an increased occurrence of the mentioned side effects, the aim of this study was to determine the effect of two different framings of informed consent on the occurrence and perceived threat of side effects in general. An active antihypertensive agent (metoprolol) was used, since the concerns of patients with hypertension about side effects often lead to discontinuation or poor adherence [16]. This highlights the potential clinical relevance of side effect framing for antihypertensive agents. The main aim was to test an informed consent

procedure, which included the standard information about the antihypertensive agent, but also described dizziness positively as an onset sensation. Participants were expected to generalize the given positive information to other specific side effects and thereby foster positive treatment expectations, which should cause side effects to be rated less threatening in the positive framing group. As a post-hoc analysis, it was investigated whether the verbally induced positive framing had a differential effect in those participants who had a rather negative treatment expectation. These participants were identified through their beliefs about medicine [17], which are directly linked to the development of side effects, e.g. in rheumatoid arthritis [18]. Patients with negative beliefs, e.g. regarding the general harm of medicine, are prone to misattribution of symptoms and hence to discontinuation of their medication [19]. As a consequence, negative beliefs about medicine predict insufficient adherence to medication [20, 21]. Therefore, it is necessary to take a closer look at these participants and their attribution of side effects after framing and drug administration.

METHODS

Study design and procedure

The study was approved by the Ethics Committee of the Medical Chamber Hessen. The main aim of the experiment was to compare the standard information on adverse side effects of metoprolol with modified information, which framed the common side effect dizziness as an onset sensation. In this “positive framing” condition, participants were told that dizziness indicated that the drug had started to take effect and might even be a sign that their body metabolizes the beta-blocker well (See Figure 1 for verbatim framings). Although four common metoprolol-specific side effects were mentioned in both framings, dizziness was the only differentially framed side effect.

Participants were randomly assigned to one group (simple randomization via http://www.randomization.com; Figure 2). The study was double-blinded, as neither participants nor the experimenter knew which condition the participant received. Participants were not informed that there were two different framing groups. Instead, they were told that psychological influences on drug effects were being investigated. The framing was delivered by an independent "study supervisor" who wore a white coat and knew which condition the participant had been assigned to. This supervisor also dispensed the medication, but was not involved in any of the subsequent experimental procedures. After the framing, all participants received 100 mg metoprolol. An exercise test on a bicycle ergometer was conducted before and after drug administration to provoke drug-attributed side effects and to clarify the drug effect on physiological data. Thereafter, subjective and objective data were assessed.

Participants

The study included healthy male participants (n=80), 18−35 years old, fluent in German language, and with a BMI between 20 and 30. Participants were excluded if they had taken beta-blockers before. Preliminary inclusion criteria were checked through a short telephone interview. Eligible participants were then invited for a one-hour examination at the private practice of the study physician, who also recorded medical history. Possible contraindications for beta-blocker intake, such as atrioventricular block, were diagnosed via electrocardiogram (ECG) and affected participants were excluded. Informed consent was obtained from all individual participants included in the study. Data collection was carried out at the Department of Psychology, University of Marburg. Participants were rewarded with €50 for full participation.

Measures

Generic Assessment of Side Effects Scale (GASE). Primary outcomes were intensity, perceived threat, and the number of drug-attributed side effects. These variables were measured with the GASE scale, a 36-item scale that includes the most common adverse events among 6,000 different drugs [22]. One item was removed because it was not applicable for the male sample (painful or irregular menstruation). Participants rate the intensity of every symptom on a four-point Likert scale ("not present" to "severe") and specify whether, in their opinion, the symptom was related to the medication (drug attribution, yes/ no). To measure perceived threat, a four-point Likert scale was added for every item analogous to the intensity ratings ("not present" to "severe"). Participants were also asked to rate whether the drug-attributed symptom was part of the desirable effect of the medication or whether it was a side effect (desirable effect/side effect). This information was used as an extended manipulation check to determine whether occurring dizziness was more often described as a side effect in the neutral framing group. To ascertain the baseline level of minor bodily symptoms, the 35 GASE items were also presented at baseline, but without asking for the drug-attribution rating (baseline symptom score). Three main scores were calculated using the GASE data: number, intensity and perceived threat of drug-attributed side effects. The total number of drug-attributed symptoms was calculated via sum scores of all symptoms that were (a) rated with an intensity >0 and (b) attributed to the drug. Overall scores of intensity and perceived threat were calculated by summing the ratings (1–4) of every drug-attributed symptom. Additionally, two medication-specific subscores were calculated for the number of side effects, intensity and perceived threat ratings: metoprolol-specific and non-specific side effects. Side effects listed as frequent in the package leaflet were considered as drug-specific: headache, dizziness, breathing problems, circulation problems, nausea, abdominal pain, vomiting, and fatigue. All other side effects were defined as non-specific for metoprolol.

Beliefs about medicines questionnaire (BMQ). The BMQ assesses individual attitudes toward medication and is usually divided into two parts: one concerned with general beliefs about medicine and the other one with individually prescribed medication [17]. As only healthy participants with no chronic medication intake were enrolled in this study, only the general beliefs part could be used. It consists of three subfacets (general harm, general overuse, and general benefit). The general harm scale focuses on medication as a source of harmful effects and is thus most relevant for the occurrence of the nocebo effects. The items are rated on a five-point Likert scale (1=strongly agree, 2=agree, 3=uncertain, 4=disagree, and 5=strongly disagree).

Physiological data. Physiological data was assessed (heart rate, systolic and diastolic blood pressure) using the Task Force Monitor™ [23] to ensure that the medication was adequately taken and to identify possible group differences in the drug effect. All physiological variables were measured at exercise on a bicycle ergometer. At least one day before drug administration, an individual workload for each participant was estimated, on which a target heart rate of 150 bpm was obtained [24]. The exercise tests were conducted prior to (pre) and after (post) drug intake. All participants started at 100 W. The workload was subsequently increased three times every 30 seconds until the predetermined individual level was reached; this was then maintained for another 90 seconds. In this individual interval, the physiological data was measured continuously and pre was compared to post.

Statistical analyses

To compare the positive and neutral framing groups after medication intake, the Student's *t*-test for independent samples was used. Moreover, paired *t*-tests were used to clarify a significant drug effect of metoprolol when comparing the heart rate and blood pressure at baseline and after drug intake. All analyses were set to test directional hypotheses and therefore

one-tailed. Before running the *t*-tests, data was checked for homogeneity of variance using Levene's test [25]. If Levene's test indicated equal variances between the framing groups, the *t*-test statistic was computed using pooled variances. In cases of assumed unequal variances, un-pooled variances and corrected degrees of freedom were used. All analyses were computed using IBM SPSS Statistics 24.

A subgroup of the sample was additionally analyzed to further investigate participants with negative beliefs about medicine and hence negative treatment expectations about the forthcoming drug intake. The Beliefs about Medicines Scale [17] was used to determine participants' pre-existing beliefs concerning the general harm of medicine. Using a median split, they were then classified into "high-harm" and "low-harm" belief groups.

RESULTS

Participant characteristics

A total of 115 volunteers were screened via phone, of which 81 were potentially eligible. One volunteer was excluded by the study physician due to health concerns. The remaining 80 healthy participants were then randomized to receive either metoprolol and a positive framing or metoprolol and a neutral framing. As described in Table 1, there were no differences in age, BMI, education or baseline symptom load between the framing groups. There were no drop-outs and all 80 participants completed the experiment. Missing data only occurred in physiological outcomes, where technical issues led to two missing values in blood pressure values and three missing values in heart rate.

Framing: Manipulation check

The framing was expected to influence the appraisal of side effects by the participants, especially if dizziness occurred. The framing groups were compared regarding the intensity of

drug-attributed dizziness in total, and the perception of drug-attributed dizziness as an adverse side effect or as a favorable effect (i.e. onset sensation). While intensity in total and ratings of dizziness as a favorable drug effect did not differ significantly between groups, participants in the neutral framing group perceived dizziness more often as an adverse side effect (t=-1.18, p=.038, d=0.40). Thus, the framing manipulation did affect the perception of dizziness by the participants. See Table 2 for details.

Drug effect

A fall in heart rate and blood pressure appeared in all participants and was evident in individual exercise tests. This indicates that the drug was taken according to the instructions. Table 3 shows the results of the paired t-tests from pre (before drug administration) and post (after drug administration) separately for the framing groups. There were no differences in drug effects between the groups. Thus, a confounding effect of drug-induced heart rate and blood pressure changes on the outcome is unlikely.

Primary outcomes

The primary objective was to compare the drug-attributed side effects between the framing groups. Three main scores were calculated using the GASE data: number, intensity and perceived threat of drug-attributed side effects. These main scores were split into two subscores each (metoprolol-specific and non-specific side effects). As shown in Table 4, the groups differed in the perceived threat of metoprolol-specific symptoms (t=-1.68, p=.049, d=0.38): participants in the positive framing group perceived drug-attributed metoprolol-specific symptoms as less threatening than the participants in the neutral framing group (Figure 3).

Referring to Cohen [26], the effect size is small. The effect size describing a potential difference between the groups concerning the perceived threat of non-specific symptoms is

similar, yet the tests did not reveal a significant difference. Additionally, there were no significant group differences in number or intensity of drug-attributed symptoms.

Subgroup analysis

The "high-harm" subsample with negative expectations concerning pharmacotherapy consisted of 45 participants (18 in the positive framing group, 27 in the neutral framing group). According to the median split procedure, the participants in this subgroup had BMQ-harm values of 9 or above. The analyses were repeated regarding the same primary outcomes as with the total sample. The framing groups differed in the number of drug-attributed metoprolol-specific symptoms (t=-2.50, p=.009, d=0.58), the intensity of drug-attributed metoprolol-specific symptoms (t=-1.88, p=.034, d=0.58) and the perceived threat of metoprolol-specific symptoms (t=-2.13, p=.021, d=0.62). In this subgroup of participants who were likely to be susceptible to nocebo effects, positive framing positively influenced the reported side effects and their interpretation (Figure 4). The significant effect sizes can be interpreted as moderate [26]. Table 5 presents the test statistics and effect sizes for all outcomes and subscores. The "low-harm" subsample (BMQ-harm <9) did not differ significantly among the framing groups in any of the described outcomes.

CONCLUSIONS

Positive framing of side effects prior to drug intake is effective in changing the appraisal of drug-specific side effects occurring in healthy participants. In the positive framing group, participants were informed about dizziness as an onset sensation, while in the neutral framing group, dizziness was described as an unpleasant, but already known side effect. Participants in the positive framing group rated drug-attributed metoprolol-specific side effects as significantly less threatening. Subgroup analyses of the participants who assume medicine to

be rather harmful revealed that this group seems to benefit from positive framing, not only regarding the perceived threat of drug-attributed specific symptoms, but also concerning the total number and intensity of specific side effects. These results strongly suggest that the positive framing, which was tested in combination with an active drug for the first time, improves the informed consent procedure. Thereby, ethical guidelines were not violated, since side effect information was genuine and complete. Particularly for participants with negative beliefs about medicine, the framing of a common side effect as an onset sensation does not only help to positively influence the side effect appraisal, but also reduces their intensity and total number of occurrences.

Remarkably, this difference in presentation of information about dizziness resulted in differences in the metoprolol-specific score, which consists of the most common side effects. Participants are assumed to generalize the given information about dizziness to other side effects, both mentioned and not explicitly mentioned specific side effects. Subgroup analysis revealed that participants who believed medicine to be rather harmful, benefited even more from positive framing. Not only did framing reduce the perceived threat of all specific side effects, but participants also reported a lower number of specific side effects with less intensity in the positive framed participants of this high-harm subgroup. Since expectation and suggestion are important factors associated with side effects [1], these participants with negative treatment expectations seem to be more responsive to verbal information about side effects. The effect of the framing used in the present study is striking, because it was caused by spoken information only, although this kind of information transfer is not as satisfactory as written medical information, e.g. in cardiology patients [27,28]. With regard to the physiological data, it was simultaneously shown that framing did not weaken the drug response. Heart rate, systolic and diastolic blood pressure were significantly lowered in both groups.

The framing approach needs further investigation to verify its clinical relevance. It should be replicated in a sample of patients with hypertension first. Hypertension is a major health issue worldwide [29], but the adherence of patients with hypertension to antihypertensive medication is poor [30]. In particular, in the field of blood pressure control, common side effects lower drug adherence [31]. It has also recently been demonstrated that positive treatment expectations in the form of placebo effects play an important role in the long-term treatment of hypertension [32]. On the other hand, side effects can be learned through classical conditioning [33] and may lead to negative treatment expectations, thus negatively impacting subsequent pharmacotherapy (nocebo effect). To address this issue, medical treatment should be personalized to maximize placebo effects, while minimizing nocebo effects [34]. While several methods for harnessing placebo effects have already been demonstrated, avoiding the nocebo effect is a major challenge in drug research. Physicians should be encouraged to personalize the informed consent procedure, e.g. when prescribing a drug, considering patients' beliefs about medicine. These beliefs could easily be assessed by questionnaire while patients are in the waiting room. Interventions, such as the described framing, could then be used to improve the informed consent procedure in patients who are more skeptical about drugs.

There are some limitations regarding the experiment that should be considered. First, the sample consisted only of healthy participants. Healthy participants might have different expectations about a drug that they are about to take compared with patients, as they expect no relief or cure for a disease. Second, only male participants were recruited to eliminate gender differences in blood pressure and blood pressure control [35]. Men are at greater risk for cardiovascular disease than women [36]. Since some participants did not experience any drug-attributed side effects, this could have led to a floor effect that weakened the framing effect. Third, the sample size of the analyzed subgroup was small (n=45) and the groups slightly

differed in sample size, which could have decreased the power of the tests, although equality of variance among the groups was checked and the degrees of freedom corrected. Taking into account these limitations regarding the sample, the results should be interpreted with caution.

There are also numerous advantages of this study. It is a double-blind randomized experimental between-group design, which carefully assessed reported drug-attributed side effects in a standardized manner. Additionally, objective data was obtained to investigate possible influences of the framing procedures on drug effects.

This is the first approach to verbal expectation manipulation via framing in antihypertensive medication and the first study to frame a common side effect as an onset sensation. The preliminary usefulness of the employed framing was demonstrated within a truthful informed consent, which might be a solution to the ethical dilemma of transparency of treatment and more side effects caused by informed consent.

COMPLIANCE WITH ETHICAL STANDARDS

The authors declare that they have not conflict of interest. All procedures performed involving human participants were in accordance with the ethical standards of the ethics committee of the Medical Chamber Hessen which approved the study and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all participants included in the study.

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TABLES

Table 1 Demographic characteristics for the *positive* and *neutral framing conditions*

	Positive framing (n=40)	*Neutral framing (n=40)*	*Group differences*	*p*
Age in years, *M* (*SD*)	24.00 (3.02)	24.95 (3.00)	*t* (78)=-1.41	.162
BMI, *M* (*SD*)	23.00 (1.94)	23.74 (1.91)	*t* (78)=-1.73	.088
Education in years, *M* (*SD*)	15.45 (2.93)	15.71 (1.91)	*t* (78)=-0.39	.695
Baseline symptom score, *M* (*SD*)	4.95 (4.62)	5.72 (5.73)	*t* (78)=-0.67	.507

Note. BMI=body mass index; M=mean; SD=standard deviation

Table 2 Drug-attributed dizziness ratings for the *positive* and *neutral framing conditions*

Outcome	*Positive framing (n=40)*	*Neutral framing (n=40)*	*Group differences*	*p*	*d*
Intensity of dizziness, *M (SD)*	0.48 (0.68)	0.60 (0.63)	*t* (78)=-0.85	.199	0.18
Dizziness as adverse side effect, *M (SD)*	0.20 (0.46)	0.42 (0.64)	*t* (78)=-1.81	.038	0.40*
Dizziness as favorable effect, *M (SD)*	0.28 (0.60)	0.18 (0.38)	*t* (78)=0.89	.189	-0.20

Note. M=mean; SD=standard deviation; *d*=Cohen's *d*; *$p<.05$

Table 3 Physiological measures of exercise tests for the *positive* and *neutral framing conditions*

Outcome	*n*	*Pre*	*Post*	*Pre-post differences*	*p*
Heart rate (bpm)					
Positive framing group *M (SD)*	38	151.71 (9.25)	114.98 (8.79)	*t* (37)=29.32	<.001
Neutral framing group *M (SD)*	38	151.62 (9.50)	112.82 (6.84)	*t* (37)=25.31	<.001
Systolic blood pressure (mmHg)					
Positive framing group *M (SD)*	37	167.17 (26.98)	125.97 (15.75)	*t* (36)=8.58	<.001
Neutral framing group *M (SD)*	37	157.95 (25.91)	125.63 (15.04)	*t* (36)=8.81	<.001
Diastolic blood pressure (mmHg)					
Positive framing group *M (SD)*	37	82.87 (9.79)	70.59 (10.36)	*t* (36)=7.45	<.001
Neutral framing group *M (SD)*	37	84.48 (9.01)	71.63 (8.72)	*t* (36)=9.05	<.001

Note. bpm=beats per minute; mmHg=millimeter of mercury; M=mean; SD=standard deviation; *p<.05

Table 4 Group differences between the *positive* and *neutral framing conditions* in GASE outcomes

Outcome	*Positive framing (n=40)*	*Neutral framing (n=40)*	*Group differences*	*p*	*d*
No. of drug-attributed side effects					
Specific side effects, *M (SD)*	1.38 (1.56)	1.75 (1.77)	*t* (78)=-1.01	.159	0.22
Non-specific side effects, *M (SD)*	0.68 (1.02)	1.15 (1.93)	*t* (78)=-1.38	.087	0.30
Intensity of drug-attributed side effects					
Specific side effects, *M (SD)*	1.60 (2.00)	1.85 (2.02)	*t* (78)=-0.56	.290	0.12
Non-specific side effects, *M (SD)*	0.83 (1.60)	1.30 (3.12)	*t* (78)=-0.86	.198	0.20
Perceived threat of drug-attributed side effects					
Specific symptoms, *M (SD)*	0.50 (1.04)	1.23 (2.53)	*t* (51.79)=-1.68	.049	0.38*
Non-specific symptoms, *M (SD)*	0.20 (0.97)	0.98 (3.27)	*t* (45.76)=-1.44	.079	0.32

Note. M=mean; SD=standard deviation; *d*=Cohen's *d*; *p<.05

Table 5 Group differences between the *positive* and *neutral framing conditions* in GASE outcomes ("high-harm" group; BMQ-harm ≥9)

Outcome	*Positive framing (n=18)*	*Neutral framing (n=27)*	*Group differences*	*p*	*d*
No. of drug-attributed side effects					
Specific side effects, *M (SD)*	0.72 (1.02)	1.81 (1.90)	*t* (41.44)=-2.50	.009	0.71*
Non-specific side effects, *M (SD)*	0.56 (0.98)	1.44 (2.22)	*t* (43)=-1.59	.060	0.51
Intensity of drug-attributed side effects					
Specific side effects, *M (SD)*	0.83 (1.15)	1.89 (2.19)	*t* (43)=-1.88	.034	0.61*
Non-specific side effects, *M (SD)*	0.89 (2.11)	1.67 (3.72)	*t* (43)=-0.80	.213	0.26
Perceived threat of drug-attributed side effects					
Specific symptoms, *M (SD)*	0.16 (.51)	1.37 (2.87)	*t* (28.46)=-2.13	.021	0.59*
Non-specific symptoms, *M (SD)*	0.39 (1.42)	1.37 (3.93)	*t* (43)=-1.01	.159	0.33

Note. M=mean. SD=standard deviation; *d*=Cohen's *d*; *p<.05

FIGURES

Positive framing	"You will now receive a beta-blocker, 100 mg of metoprolol. There are some frequently co-occurring symptoms, which you should be informed about. Frequently, in this case, means that the side effects occur in 10 persons out of 100. These side effects include headache and stomach pain or nausea. Often a feeling of dizziness also occurs. ***This is a sign that the drug is starting to work. If you become dizzy after taking the medication, it means that your body is responding to the beta-blocker particularly well.*** In any case, please inform us of any co-occurring symptoms during the trial."
Neutral framing	"You will now receive a beta-blocker, 100 mg of metoprolol. There are some frequently co-occurring symptoms, which you should be informed about. Frequently, in this case, means that the side effects occur in 10 persons out of 100. These side effects include headache and stomach pain or nausea. Often a feeling of dizziness also occurs. ***This is a potentially unpleasant, but already known side effect of the drug.*** In any case, please inform us of any co-occurring symptoms during the trial."

Figure 1 Framings used in the experiment

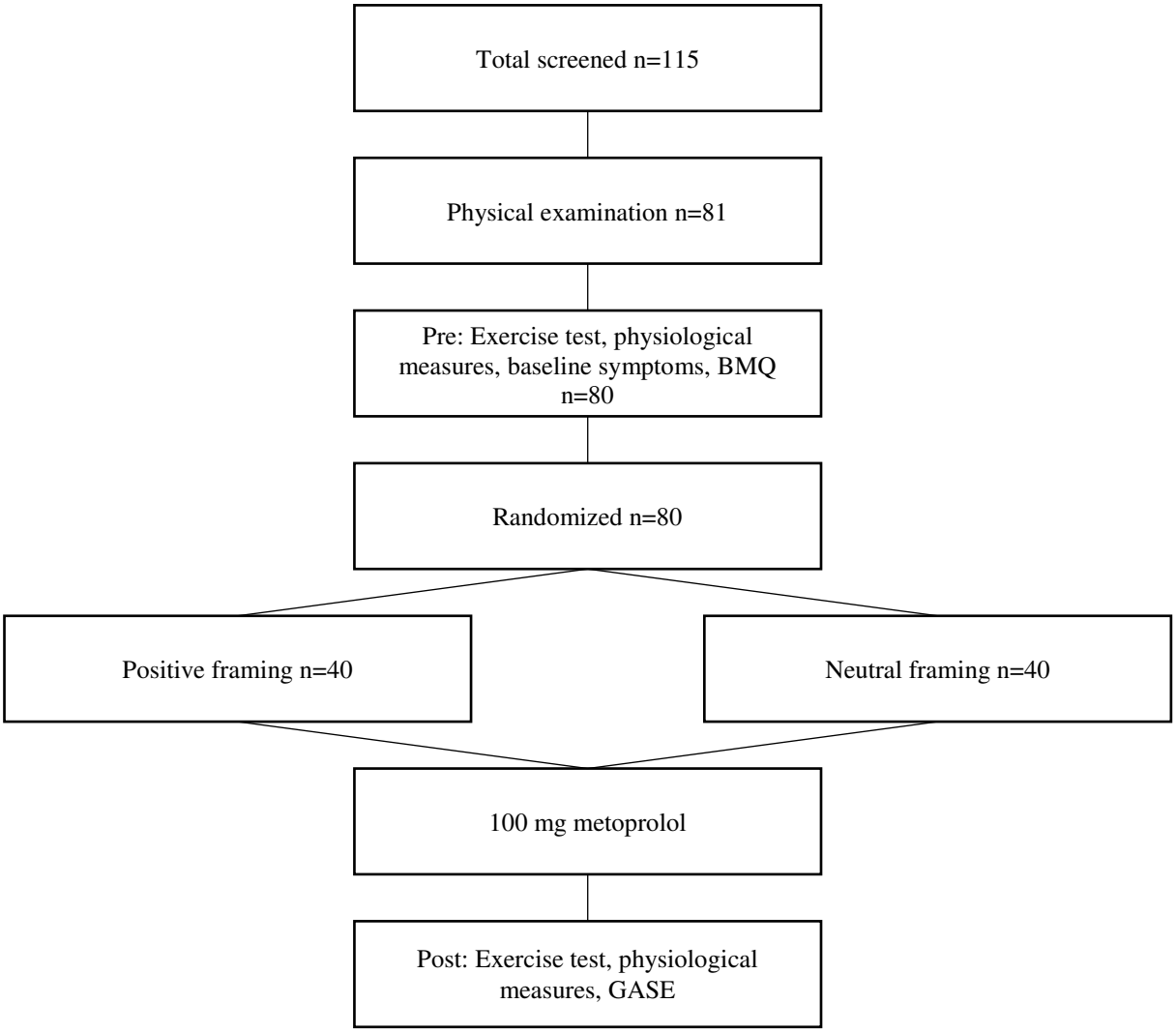

Figure 2 Experimental design

Note. BMQ=Beliefs about Medicine Questionnaire; GASE= Generic Assessment of Side Effects Scale

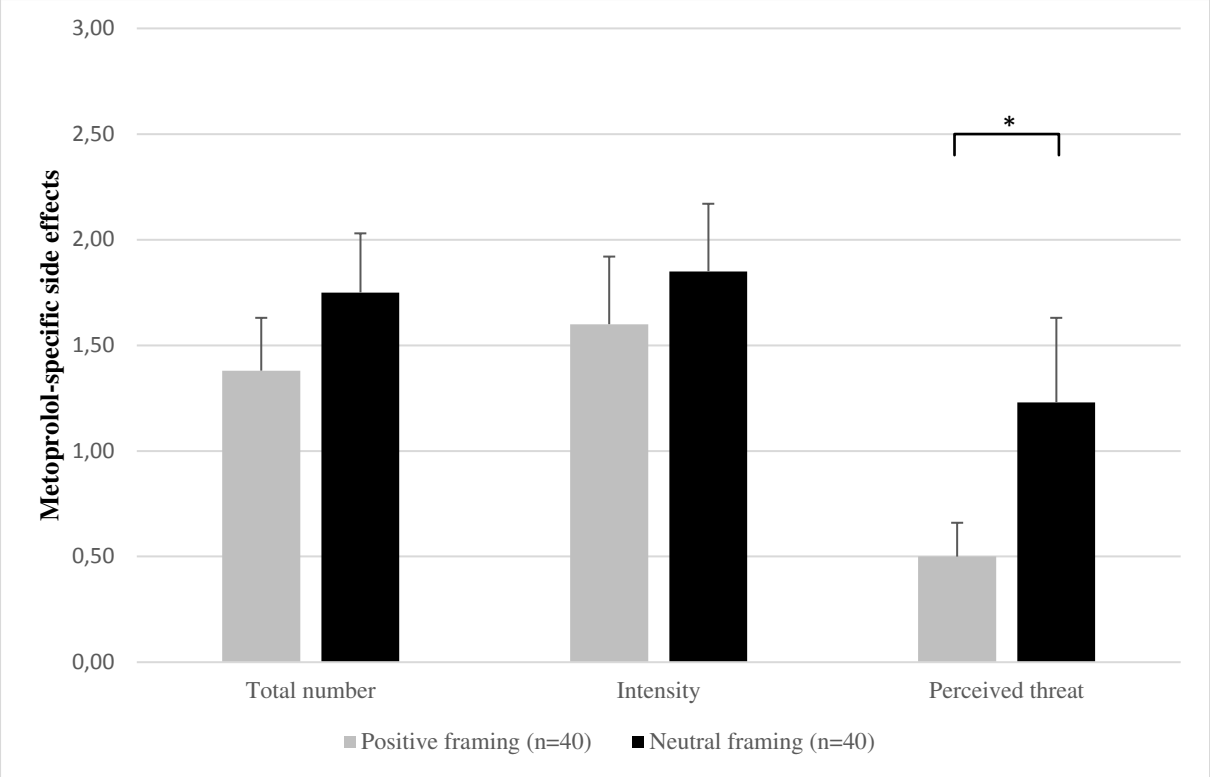

Figure 3 Specific drug-attributed side effect outcomes

Note. *p<.05

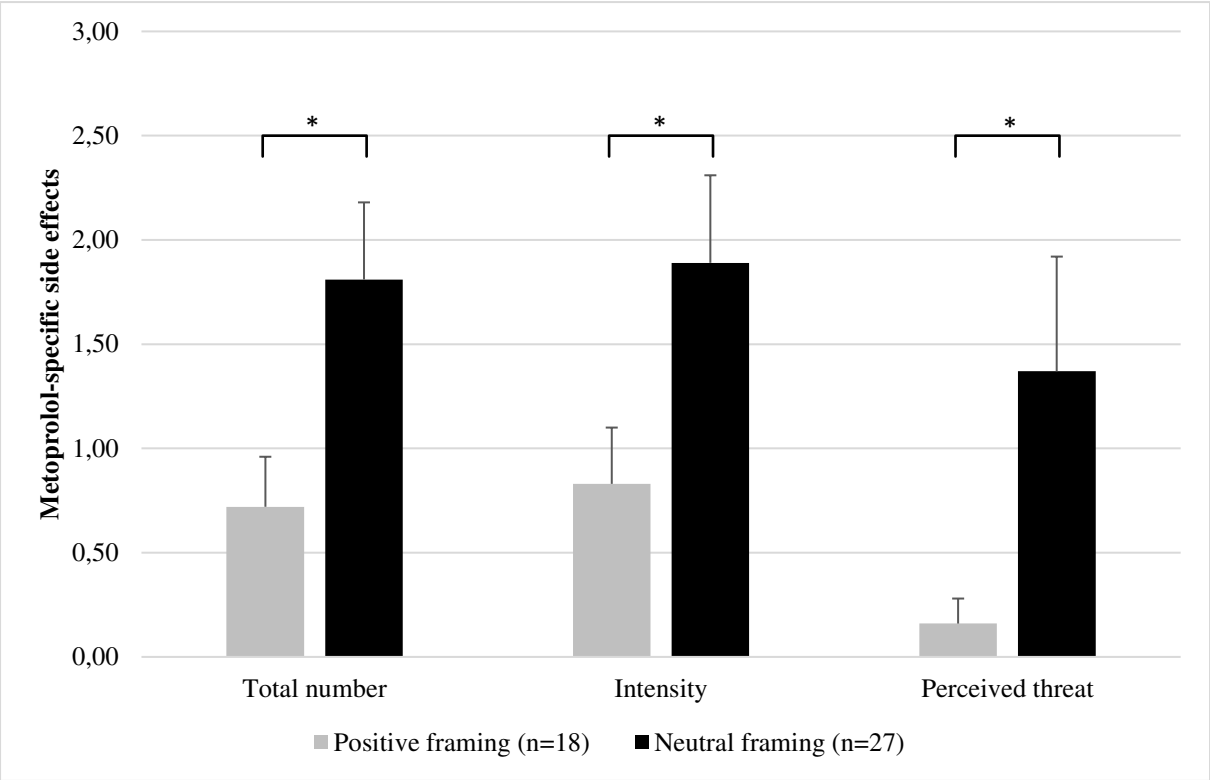

Figure 4 Specific drug-attributed side effect outcomes ("high-harm" group; BMQ-harm ≥9)

Note. *p<.05

A.3 Studie 3

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IT'S ALL A MATTER OF NECESSITY AND CONCERN:

EXPLAINING ADHERENCE IN HYPERTENSION

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Abstract

Objective: Hypertension is often treated pharmacologically, yet drug adherence is poor. Beliefs about the specific antihypertensive medicine, i.e., beliefs about its benefits and also concerns about relevant risks (necessity-concern framework; NCF) could be key to increasing adherence. Previous studies have investigated the NCF as independent predictors among other adherence-related variables; the present study investigates the mediating role of the NCF.

Methods: Patients with hypertension (n = 273) were surveyed online about demographics, health- and treatment-related factors, control beliefs, necessity and concern beliefs about their antihypertensive medication, and adherence. The data were analyzed using structural equation modeling (SEM).

Results: Necessity was positively (β = .26, p = .009) and concern was negatively (β = -.51, p = .020) associated with adherence. The NCF mediated the influence of background variables on adherence. Necessity was associated with comorbidity (β = -.36, p < .001), treatment time (β = .19, p = .004), emotionally supportive doctor-patient communication (β = .12, p = .045), side effects (β = .16, p = .013), personal control (β = -.13, p = .022), and treatment control (β = .29, p < .001). Concern was associated with side effects (β = .38, p < .001) and beliefs about medicine in general being harmful (β = .61, p < .001). The model was of acceptable fit (RMSEA = 0.61), explaining 23% of variance in adherence.

Conclusions: The necessity of and concerns about specific antihypertensive medication were identified as significant mediating factors directly associated with drug adherence. A personalized, emotionally supportive doctor-patient communication could be key to addressing beliefs about medicine, and therefore to increasing adherence.

Keywords: drug adherence; antihypertensive medication; beliefs about medicine; structural equation modeling; doctor-patient communication.

Introduction

Hypertension is a major health issue which affects approximately one billion adults worldwide (Kearney et al., 2005). Patients with hypertension require blood pressure control to prevent cardiovascular events, as well as cardiovascular and kidney diseases (Chobanian et al., 2004; Sundström et al., 2015). Lifestyle adjustments (exercise, change in nutrition, e.g., less fat, less salt) are recommended for all individuals with hypertension (WHO, 2003). Additionally, antihypertensive drugs are often prescribed to lower the patients' blood pressure instantly (Mancia et al., 2013).

Unfortunately, adherence to blood pressure medication is poor (Naderi, Bestwick, & Wald, 2012). Adherence describes the extent to which a patient's health behavior (e.g., taking antihypertensive medication) reflects a health plan that was jointly set up by the patient and the clinician (Gould & Mitty, 2010). A major obstacle to achieving satisfactory adherence in patients with hypertension is that hypertension rarely causes noticeable symptoms (Kjellgren, Svensson, Ahlner, & Säljö, 1997), while antihypertensive drugs can cause side effects that lower drug adherence (Vegter, De Boer, Van Dijk, Visser, & De Jong-Van Den Berg, 2013). This contrast is particularly important since the patients do not feel any relief by taking the medication but are advised to take them for an indefinite time. Patients who are not completely adherent often fail to achieve blood pressure control and are falsely categorized as patients with resistant hypertension (Jung et al., 2013); thus, they do not receive optimal care.

Health behavior in chronic illness has been conceptualized in various models, e.g., the Health Belief Model (Rosenstock, 1974), the Common-Sense Model of Illness Representation (Diefenbach & Leventhal, 1996) or the Self-Regulatory Model (Leventhal, Diefenbach, & Leventhal, 1992; Leventhal, Nerenz, & Steele, 1984). In the field of drug treatment of chronic illnesses, these models can be used to illustrate how patients decide to engage in health behavior (i.e., adherence to the pre-agreed treatment plan). A widely recognized model to explain these

conscious processes prior to adherent behavior is the necessity-concern framework (NCF; Horne, Weinman, & Hankins, 1999). The NCF postulates that patients' key beliefs about a medical treatment determine their common-sense evaluation and thus, the extent of adherence. These beliefs primarily consist of two categories: the patients' perception of how much they need the specific treatment (necessity beliefs) and concerns about adverse effects of that treatment (concern beliefs). The NCF is well established and has been applied to adherence in over 30 different conditions, including to cardiovascular diseases (Foot, La Caze, Gujral, & Cottrell, 2016). Various cross-sectional analyses have investigated the contribution of beliefs about necessity and concern to adherence in hypertension (Maguire, Hughes, & McElnay, 2008; Ross, Walker, & MacLeod, 2004b; Ruppar, Dobbels, & De Geest, 2012). All these studies included necessity and concern in regression models as two predictors among many other variables. In hypercholesterolemia, Berglund, Lytsy, and Westerling (2013) assumed that the NCF is a central construct in the explanation of variance in adherence, mediating the influence of other predictors. While this mediating influence of necessity could be demonstrated, the role of concern remained rather unclear.

The mediating influence of the NCF on adherence in cardiovascular-related long-term treatment has been exploratorily investigated. To prove its applicability in hypertension, a confirmatory analysis is necessary. The previously assumed structure of factors was therefore transferred with minor adjustments to the treatment of hypertension, regarding adherence to antihypertensive medication. The following important background variables were included in the model since they are factors that are already known to be associated with adherence in cardiovascular diseases. First, demographic variables such as higher age (Briesacher, Andrade, Fouayzi, & Chan, 2008), female gender (Krousel-Wood et al., 2011), and higher education (Lowry, Dudley, Oddone, & Bosworth, 2005) are related to a higher drug adherence. Secondly, a higher adherence is connected with numerous health- and treatment related factors:

comorbidities (e.g., diabetes mellitus; Lowry et al., 2005), and treatment perception, i.e., general beliefs about medicine (Horne & Weinman, 1999). Another influential treatment-related factor appears to be the "explanation satisfaction" of patients—i.e., how satisfied they are with their physician's explanation regarding their illness and treatment options (Berglund et al., 2013). The key to a satisfactory explanation could be patient-centered communication, which is also linked to adherence (Marshall, Wolfe, & McKevitt, 2012). Berglund et al. (2013) also included health locus of control in their structural equation model, which was significantly associated with the NCF.

Although many individual factors of adherence to antihypertensive drugs have already been identified, this study aimed to integrate all these assumed factors in a coherent model which would allow a comparison of the different adherence-related variables with regard to their importance. Therefore, the model described by Berglund et al. (2013) was transferred from hypercholesterolemia to a hypertensive sample where no confirmatory model has been published so far. Additionally, the model was improved by replacing "explanation satisfaction" by a more differentiated measure of emotionally supportive doctor-patient communication. This study is the first to provide a confirmatory analysis of a previously established model in order to prove the relevance of the NCF in adherence to antihypertensive medication.

Methods

This article adheres to the reporting standards for structural equation modeling (SEM) established by Schreiber, Nora, Stage, Barlow, and King (2006).

Sampling

The study was approved by the ethics committee of the Department of Psychology at Philipps-University Marburg. Data collection was carried out online via Unipark

(https://www.unipark.de). The online survey was active from June 2016 to January 2017; the link to participation was published in online forums and spread via various mail distributors (e.g., the German Society for Hypertension). The link was also printed on flyers which were distributed to pharmacies and hospitals. To be included, participants must have been 18 years or older and must have received a prescription for antihypertensive medication at least once in their lifetime. Potential participants were informed that for participation in the study whether they were still taking their medication was not important. The first page of the survey explained precisely the purpose of the study. Further, participants were informed that their data was transmitted encrypted and anonymously. Participants could then click a button to give their informed consent. At the end of the survey, a mailing address could be entered independently from the other data to participate in a prize draw of four 50€ vouchers for an online retailer.

A total of 515 participants provided informed consent. Of these, 161 dropped out directly after the informed consent, and did not provide any data. Another 81 participants dropped out before finishing the survey (mean age: 48 years; 51% female). The remaining 273 completers were checked for inclusion criteria and plausibility of answers and were all included in the analysis.

Measures

Rief adherence index (RAI). The RAI is a four-item self-report scale to assess drug adherence (Glombiewski, Nestoriuc, Rief, Glaesmer, & Braehler, 2012). The items are formulated as statements describing non-adherent behavior. Participants have to rate these statements on a five-point Likert scale: 1 = (almost) never happened, 2 = rarely happened (in 20–40% of cases), 3 = often happened (in 40–60% of cases), 4 = happened most of the time (in 60–80% of cases), and 5 = (almost) always happened (in 80–100% of cases). Before answering

the RAI, participants were instructed to consider all past behaviors concerning their antihypertensive medication.

Beliefs about medicines questionnaire (BMQ). The BMQ assesses individual attitudes toward medication and is usually divided into two parts: one part is focused on individually prescribed (specific) medication and the second part is aimed at beliefs about medicine in general (Horne et al., 1999). The specific medication part consists of the scales necessity and concern, which represent the NCF for antihypertensive drugs. Participants were asked to answer these items with regard to their beliefs about their individual antihypertensive medication. The general part consists of three subfacets (general harm, general overuse, and general benefit). The general harm scale focuses on medication as a source of harmful effects. All items are rated on a five-point Likert scale (1 = strongly agree, 2 = agree, 3 = uncertain, 4 = disagree, and 5 = strongly disagree).

Generic assessment of side effects scale (GASE). The GASE is a 36-item scale that includes the most common side effects among 6,000 different drugs (Rief, Glombiewski, & Barsky, 2009). Participants rate the intensity of every symptom on a four-point Likert scale ("not present" to "severe") and specify whether, in their opinion, the symptom was related to their antihypertensive medication (drug attribution, yes/no). The intensity score of drug-attributed symptoms is calculated by summing the ratings (0–4) of every antihypertensive drug-attributed symptom.

Preference-matching scale. To operationalize patients' communication preferences, the Communication Preferences of Patients with Chronic Illness Questionnaire (KOPRA; Farin, Gramm, & Kosiol, 2011) and the Communication Behavior Questionnaire (KOVA; Farin, Gramm, & Schmidt, 2012) were used. Both questionnaires consist of the same four scales (emotionally supportive communication, effective and open communication, communication about personal circumstances and patient participation, and patient

orientation). While KOPRA asks for patients' preferences, KOVA assesses the patients' evaluation of their physicians' real behavior. The items are designed in parallel and can be matched to calculate a score that expresses the fit of preferences and the actual shown behavior of the physician. The scores range from -14 (preference item: extremely important, behavior item: strongly disagree, indicating the worst fit) to 14 (preference item: extremely important, behavior item: strongly agree, indicating a perfect fit). The preference-matching items are highly correlated with patient satisfaction and trust in the physician. The emotionally supportive communication scale (ESC) is one of four preference-matching scales. It can be considered the most relevant preference scale since it has been shown to have the highest construct validity (Farin et al., 2012). Therefore, the ESC scale was the only scale included in the analysis. Participants were advised to refer to their antihypertensive medication and the physician who prescribed it.

Brief illness perception questionnaire (Brief IPQ). The Brief IPQ assesses illness perceptions in eight dimensions: consequences, timeline, identity, personal control, treatment control, emotional representation, concern, coherence (Broadbent, Petrie, Main, & Weinman, 2006). Each dimension is rated for an item from 0 to 10. To match the model of Berglund et al. (2013), the control items of the Brief IPQ were included in the structural equation model. The participants were instructed to refer to hypertension when answering the questionnaire.

Data Analysis

Based on the model by Berglund et al. (2013), SEM was used to relate the variables described. SEM is a procedure that combines regression equations with the concept of confirmatory factor analysis (CFA), allowing the integration of more than one regression into one model. This model can then be evaluated using several goodness-of-fit indices, which indicate how well the conceptualization of a theory fits the collected data. SPSS AMOS

(Arbuckle, 2016) was used for SEM in the dataset. All parameters were estimated using maximum likelihood (ML), which is the most common method in SEM. Well-established goodness-of-fit indices of SEM are the chi-square test, the comparative fit index (CFI) and the root mean square error of approximation (RMSEA; Kline, 2011). For the CFI, values of > 0.95 are generally accepted; the RMSEA value and its confidence interval should not exceed 0.08 for an acceptable model fit of data (Schreiber et al., 2006).

Research Framework

The previously described adherence framework model by Berglund et al. (2013) was reconstructed containing the necessity-concern framework as mediating variable and adherence as dependent variable (Figure 1). Nine variables were included as independent, and were derived from the three categories that are included in the model: demographics, health- and treatment-related factors, and health control variables. The present study did not include occupation as a background variable since it is not a factor in other studies investigating the NCF and adherence to antihypertensive drugs (Horne, Clatworthy, & Hankins, 2010; Maguire et al., 2008; Phatak & Thomas, 2006; Rajpura & Nayak, 2014; Ruppar et al., 2012).

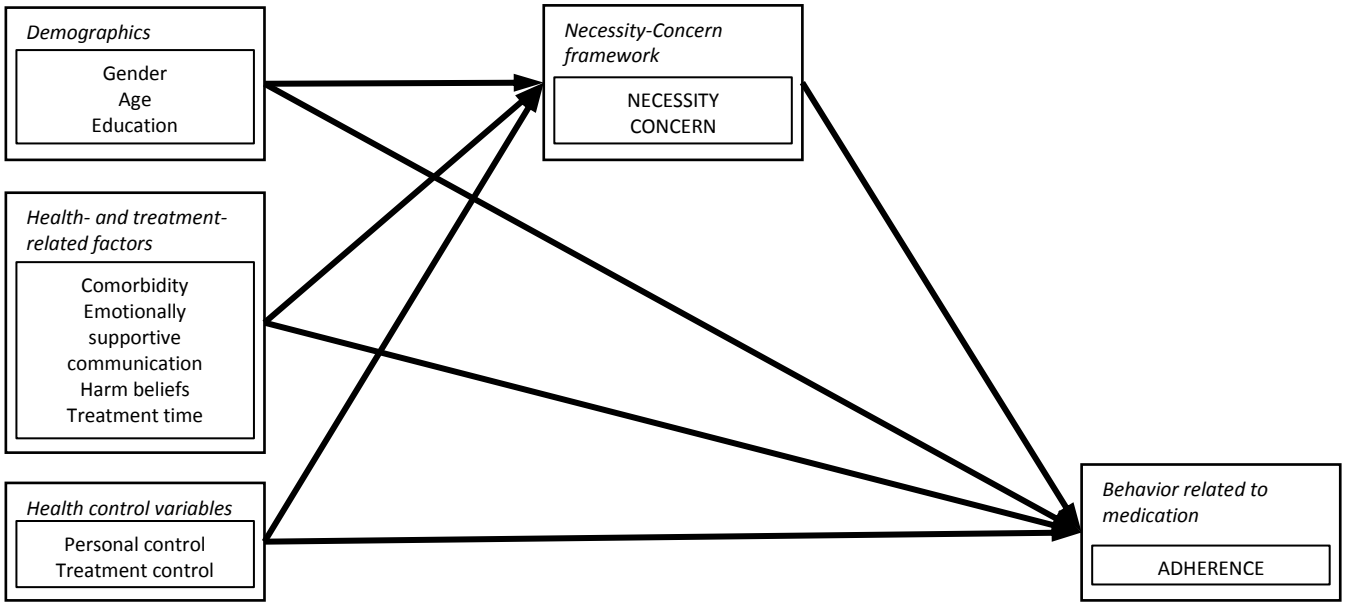

Figure 1. Research framework.

Results

Data Description

SEM was based on the data of 273 participants. There were no missing values in the analyzed variables except for treatment time (n = 4). Multivariate normality of the variables was slightly violated, presumably due to the low intensity of side effects and the high adherence assessed with the RAI (see Table 1 for means and standard deviations). ML tends to be robust even in non-normal data (Boomsma & Hoogland, 2001; Curran, West, & Finch, 1996; Diamantopoulos & Siguaw, 2000). No multivariate outliers were identified. All variables were checked regarding multicollinearity, which did not occur (see Table 2 for correlations).

Table 1

Demographic Characteristics of the Total Sample (n = 273)

Variable	N	Result
Age, years, mean (SD)	273	53.93 (15.46)
Gender, male, %	133	51.28
Upper secondary education, %	233	85.35
Antihypertensive medication, %	273	
ACE inhibitor	82	30.00
AT1 receptor blocker	135	49.45
Beta blocker	128	46.88
Calcium channel blocker	90	32.96
Diuretic	140	29.30
Comorbidity, yes, %	160	58.61
No. of different agents, mean (SD)	273	1.89 (1.03)
Treatment time, months, mean (SD)	269	108.44 (107.11)
ESC matching, mean (SD)	273	9.76 (15.06)
GASE, mean (SD)	273	2.63 (5.08)
B-IPQ personal control, mean (SD)	273	5.69 (2.43)
B-IPQ treatment control, mean (SD)	273	7.66 (2.08)
Harm, mean (SD)	273	8.97 (2.78)
Necessity, mean (SD)	273	17.78 (4.16)
Concern, mean (SD)	273	14.84 (4.28)
RAI, mean (SD)	273	14.67 (2.19)

Note. Patients were allowed to report more than one antihypertensive medication; therefore N and % do not add up to 100%. SD = standard deviation; ACE = angiotensin converting enzyme; AT = angiotensin; ESC = emotionally supportive communication; GASE = generic assessment of side effects scale; B-IPQ = brief illness perception questionnaire; RAI = Rief adherence index.

Table 2

Correlation Analysis for Structural Equation Model Variables

Variable	1	2	3	4	5	6	7	8	9	10	11	12
1. Age	1	-	-	-	-	-	-	-	-	-	-	-
2. Gender	0.32**	1	-	-	-	-	-	-	-	-	-	-
3. Education	0.01	0.09	1	-	-	-	-	-	-	-	-	-
4.Comorbidity	0.17**	-0.09	-0.08	1	-	-	-	-	-	-	-	-
5. Treatment time	0.43**	0.19**	0.03	0.18**	1	-	-	-	-	-	-	-
6. ESC matching	0.04	0.04	0.03	-0.02	0.12	1	-	-	-	-	-	-
7. Side-effect intensity	-0.07	-0.17**	-0.28**	0.18**	0.04	-0.00	1	-	-	-	-	-
8. Personal control	0.11	0.15*	-0.02	-0.13*	0.05	-0.01	-0.14*	1	-	-	-	-
9. Treatment control	0.06	0.13*	0.18**	-0.09	0.08	0.18**	-0.24**	0.15*	1	-	-	-
10. Harm	0.05	-0.22*	-0.12*	0.12	-0.06	-0.13*	0.25**	-0.00	-0.33**	1	-	-
11. Necessity	0.21**	0.01	-0.02	0.39**	0.29**	0.16**	0.17**	-0.13*	0.21**	-0.05	1	-
12. Concern	0.13**	-0.18**	-0.17**	0.24**	0.09	0.13*	0.48**	-0.12*	0.32**	0.55**	0.30**	1
13. Adherence	0.02	0.08	0.04	-0.03	0.08	0.12	-0.11	-0.05	0.21**	-0.26**	-0.18**	-0.19**

Note. This correlation matrix has been calculated with Pearson's significance test (two-tailed). Indices were used for ESC matching, side-effect intensity, harm, necessity, concern and adherence. Gender is coded as 1 = male, 2 = female; SD = standard deviation; ESC = emotionally supportive communication; GASE = generic assessment of side-effects scale.

Model fit

The model fitted the data acceptably. The chi-square test was significant, $X^2(365) = 731.2$. Since the chi-square test tends to reject presented models in the face of large samples, a chi-square ratio should be calculated. The ratio of X^2 to degrees of freedom should be ≤ 2, which is fulfilled in this case (Schreiber et al., 2006). The RMSEA is .061 within a 90% confidence interval between .054 and .067, which is therefore acceptable. The CFI is .87, which is below the cut-off. The CFI is mostly used as an index of comparison to evaluate models of different data sets. Since this is the first SEM approach in this specific area, future studies must collect new data to propose model structures with a better fit. The model explained 38% of the variance in necessity, 76% of variance in concern, and 23% of the variance in adherence (Figure 2).

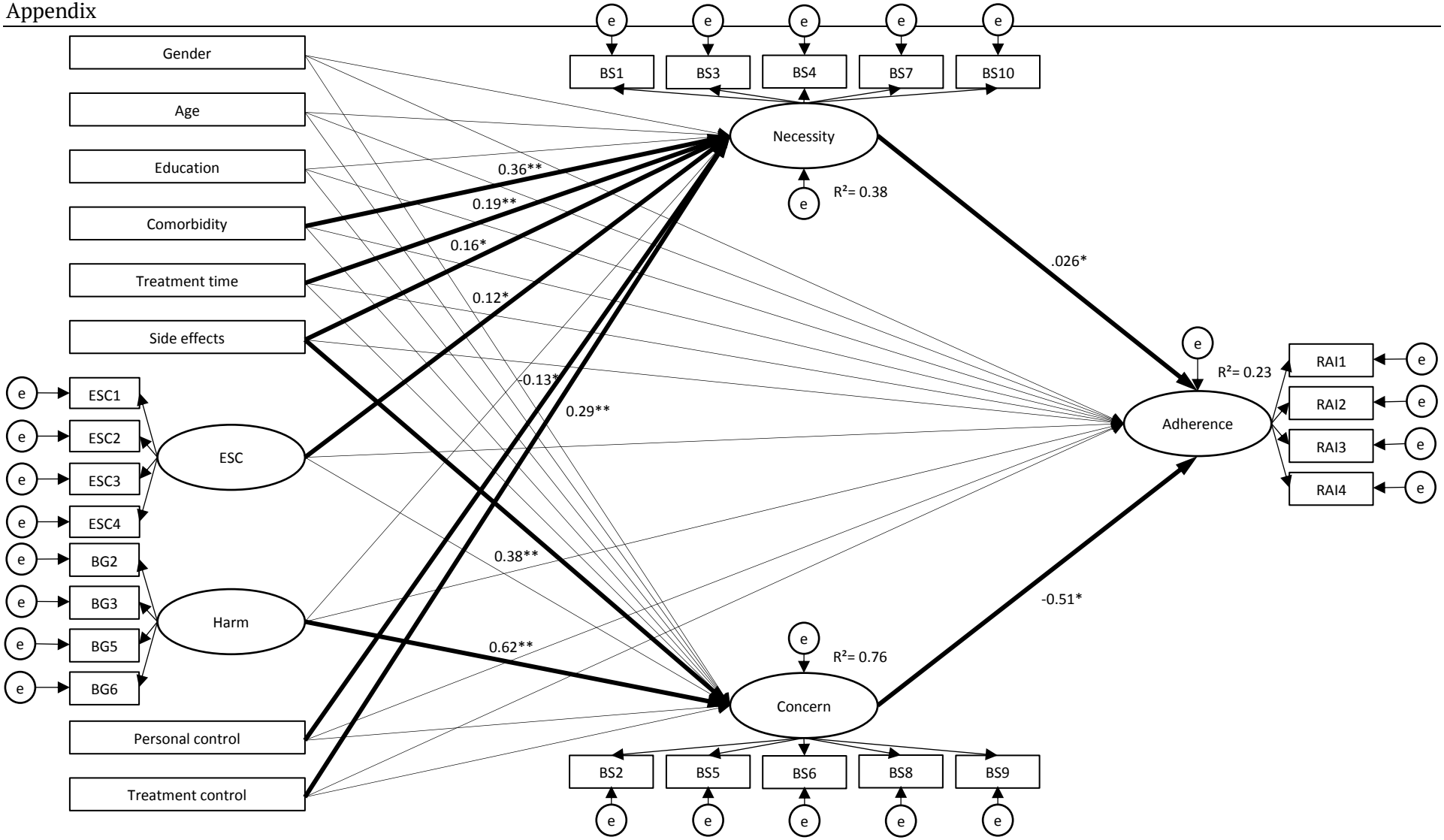

Figure 2. SEM analysis, calculated via maximum likelihood estimation, all path coefficients standardized (β). The model displays background variables and their effects on necessity and concern (regarding the prescribed antihypertensive medication) and the effects of all variables on adherence. Manifest variables are rectangles, latent constructs, ovals. Significant paths (*$p < .05$, ** $p < .001$) are presented in bold lines. R^2 displays the percentage of variance in the endogenous variables explained by the model. e = error, ESC = emotionally supportive communication (preference-matching scale), BG = beliefs general, BS = beliefs specific (beliefs about medicine questionnaire), RAI = Rief adherence index.

SEM analysis

Both constructs of the NCF were significantly related to adherence (Table 3). The belief that the prescribed antihypertensive medicine is necessary was positively associated (standardized coefficient $\beta = .26$, $p = .009$), and concerns about the medication were negatively associated with adherence ($\beta = -.51$, $p = .020$). Necessity was significantly linked to the background variables' comorbidity ($\beta = -.36$, $p < .001$), treatment time ($\beta = .19$, $p = .004$), preference-matching of emotionally supportive communication ($\beta = .12$, $p = .045$), side effects ($\beta = .16$, $p = .013$), personal control ($\beta = -.13$, $p = .022$), and treatment control ($\beta = .29$, $p < .001$). Concern was significantly associated with side effects ($\beta = .38$, $p < .001$) and the belief that medicine in general is harmful ($\beta = .61$, $p < .001$). None of the described background variables were directly associated with adherence when investigated within the NCF model.

Table 3

Path Coefficients and P-Values of Direct Effects on Necessity, Concern, and Adherence.

Background variables	Mediating variables						Dependent variable		
	Necessity			Concern			Adherence		
	β	*B*	*SE*	*β*	*B*	*SE*	*β*	*B*	*SE*
Gender	0.02	0.01	0.05	0.03	0.05	0.10	0.02	0.01	0.04
Age	0.09	0.00	0.00	0.03	0.00	0.00	0.03	0.00	0.00
Education	-0.05	-0.01	0.01	0.03	0.01	0.01	-0.03	-0.01	0.01
Comorbidity	0.36**	0.27	0.06	0.09	0.17	0.09	-0.10	-0.06	0.05
Treatment time	0.19**	0.00	0.00	0.03	0.00	0.00	0.02	0.00	0.00
ESC matching	0.12*	0.01	0.01	-0.08	-0.02	0.01	-0.03	0.00	0.01
GASE	0.16*	0.01	0.01	0.38**	0.07	0.01	0.08	0.00	0.01
Personal control	-0.13*	-0.21	0.01	-0.08	-0.03	0.01	-0.09	-0.01	0.01
Treatment control	0.29**	0.05	0.01	-0.07	-0.03	0.02	0.10	0.01	0.01
Harm	0.11	0.06	0.04	0.61**	0.84	0.12	0.13	0.05	0.08
Necessity							0.26*	0.20	0.08
Concern							-0.51*	-0.16	0.07

Note. The table shows standardized path coefficients (*β*), with *p*-values for the significance tests of all background variables on necessity, concern, and of all considered variables on adherence. ESC = emotionally supportive communication; GASE = generic assessment of side effects scale; B-IPQ = brief illness perception questionnaire;
* $p < .05$, ** $p < .001$

Discussion

The NCF was able to prove its importance regarding drug adherence of patients with hypertension. The perceived necessity of the specific medication was associated with higher adherence, while patients with concerns regarding the medication were less adherent. The standardized coefficients implicate that the emotional path via concerns was more influential. This is rather uncommon in studies that referred to the association of the NCF and adherence across various medical conditions (Foot et al., 2016). A possible explanation is that patients with hypertension rarely feel symptoms of their condition while experiencing side effects of antihypertensive medication that they are obliged to take for an unlimited amount of time (Dowell, Jones, & Snadden, 2002; Kjellgren et al., 1997). Subsequently, patients do not feel any relief from taking the medication and in this constellation, it seems plausible that concerns regarding the antihypertensive agent outweigh the influence of the perceived necessity of treatment.

None of the background variables were directly linked to adherence, while most of them were associated with at least one pathway of the NCF, thus indicating indirect effects on adherence. Participants who reported at least one comorbidity found their medication to be more necessary. The patients' beliefs that their medication was necessary were stronger the longer their treatment time. It is argued that a longer treatment time and the presence of comorbid diseases represent the severity of health impairments and therefore a higher risk of subsequent cardiovascular disease. As a consequence, these patients might engage in higher adherence to risk-lowering antihypertensive treatment (Berglund et al., 2013).

A higher preference matching of emotionally supportive communication was also accompanied by a higher perceived necessity. While Berglund et al. (2013) used "explanation satisfaction" to assess the doctor-patient communication, the present study included a slightly more tangible construct. The quality of doctor-patient communication is a very important factor

in the medication adherence of patients with hypertension and, as a consequence, in blood pressure control (Yiannakopoulou, Papadopulos, Cokkinos, & Mountokalakis, 2005).

As already demonstrated in a previous NCF adherence study with hypertensive patients, a higher personal control was accompanied by a lower perceived necessity of the medication (Ross, Walker, & MacLeod, 2004a). In contrast to other conditions, this is reasonable for many patients with hypertension: since lifestyle modifications can be sufficient for blood pressure control (Appel et al., 2003), a high personal control would indeed lower the perceived necessity of medical treatment but could also lead to a higher adherence to lifestyle changes.. Simultaneously, a higher treatment control was associated with a higher necessity for medication, which seems plausible in this context.

Concerns about the medication were positively associated with beliefs about medicine in general being harmful. This confirms findings in patients with hypertension by Ross et al. (2004). Interestingly, the intensity of side effects was associated with higher necessity as well as higher concern about the medication. While a connection between concerns about the specific medication and its side effects was already assumed in the first publication of the BMQ (Horne et al., 1999), the positive association of perceived necessity and intensity of side effects remains unexplained. A possible interpretation is that minor side effects may sometimes have paradoxically positive effects regarding the patients' treatment expectations, e.g., by signaling the potency of the medication (Rief & Glombiewski, 2012). Taking into account both indirect effects of side effects on adherence, the negative pathway via concern outweighs the positive path via necessity, which is in line with previous research (Vegter et al., 2013). There were no significant associations between demographic variables and the NCF.

The factors in the model described explained 23% of variance in adherence, which can be interpreted as high, especially compared to a previous study on patients with hypertension (11.4%; Maguire et al., 2008). This also confirms the assumption that the beliefs about medicine

account for around one-fifth of variance in adherence to medication in chronic illness (Horne & Weinman, 1999).

This is the first confirmatory approach to explain drug adherence in patients with hypertension using SEM. It is not only completely guided by theory; the model structure was also parallel to a study on another disease (Berglund et al., 2013). The structure was transferred from hypocholesteremia to patients with hypertension, making only minor adjustments. This confirmatory model allows looking at more complex relationships than the previously published regression analyses in studies of adherence to antihypertensive agents. Additionally, the inclusion of latent constructs (free of measurement errors) instead of sum scores provides a higher reliability of the analysis. The fit indices were acceptable with the exception of the comparative fit index, which at least provides a benchmark for future SEM approaches in adherence research regarding antihypertensive drugs. Due to the high anonymity of internet surveys, participants tend to answer personal questions more truthfully and their answers are not as biased by social desirability (Joinson, 1999; Richman, Kiesler, Weisband, & Drasgow, 1999), which is a great advantage in investigating adherence.

While many approaches attempt to directly improve adherence, modifying the underlying beliefs about medicine, primarily the necessity and concerns regarding the specific medication, should be considered. A higher perceived necessity—which has already been recommended to increase adherence—could be established by improving the quality of communication in health care (Osterberg & Blasche, 2005). Taking into account that in the present study the doctor-patient communication was positively associated with necessity, it seems to be a plausible starting point, as it is one of the few background variables which may be manipulated. Thus, longitudinal and particularly experimental designs are required to confirm this manipulability specifically and the mediating role of the NCF in the matter of drug adherence of patients with hypertension in general.

With regard to reducing perceived concerns about medications, previous research has mainly focused on adjustments in the information about potential side effects (Heisig, Shedden-Mora, Hidalgo, & Nestoriuc, 2015; Zikmund-Fisher, Fagerlin, Roberts, Derry, & Ubel, 2008). These adjustments could help especially those patients who have negative treatment expectations. This would highlight the described findings on harm beliefs being strongly associated with concern about the specific medication and therefore indirectly unfavorable for adherence. According to these findings and the present model, particularly addressing patients who have high harm-beliefs with specially tailored information might decrease their concerns about their medication and thus improve their adherence.

Influential background variables that cannot be manipulated could at least inform health-care professionals whether a closer look at the NCF and adherence of a patient with hypertension could prove beneficial (i.e., no comorbidity, recently started medication). Other attitudes towards medication (harm beliefs, personal and treatment control) could be directly addressed after the patient is diagnosed with hypertension, choosing an emotionally supportive approach.

Some limitations of the present study have to be considered. First, the cross-sectional design does not allow casual conclusions to be drawn. Second, all data was assessed via online self-report measures. Possible misperceptions of the participants (e.g., over- or underestimation of adherence) are as possible as limited variance due to self-selection of the sample, mainly because the inclusion criteria, such as prescribed antihypertensive agents, could not be externally verified. This could have led to a higher adherence in the sample compared to previous findings in the German population (Glombiewski et al., 2012).

To conclude, this study was able to identify the perceived necessity of and the concerns about the specific antihypertensive medication as significant factors directly associated with drug adherence. It was also shown that health-control beliefs, as well as health- and treatment-related factors, particularly the preference-matching of emotionally supportive doctor-patient

communication, have an indirect association with adherence through the NCF. This leads to the conclusion that it is necessary to focus on these specific aspects of doctor-patient communication and to assess and address the beliefs about antihypertensive medication during treatment in a personalized manner.

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Conflicts of Interest and Source of Funding

All authors have no conflicts of interest to declare including any financial, personal or other relationships with other people or organizations that could inappropriately influence, or be perceived to influence, the present work. This study was approved by the ethics committee of the Psychology Department, Philipps-University of Marburg.

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C. Eidesstattliche Erklärung:

Ich versichere, dass ich meine Dissertation

„Psychologische Aspekte der Bluthochdruckbehandlung – Einstellungen, Placebo- und Noceboeffekte“

selbstständig ohne unerlaubte Hilfe angefertigt und mich dabei keiner anderen als der von mir ausdrücklich bezeichneten Quellen und Hilfen bedient habe.

Die Dissertation wurde in der jetzigen oder einer ähnlichen Form noch bei keiner anderen Hochschule eingereicht und hat noch keinen sonstigen Prüfungszwecken gedient.

Marburg, Juni 2017 Marcel Wilhelm