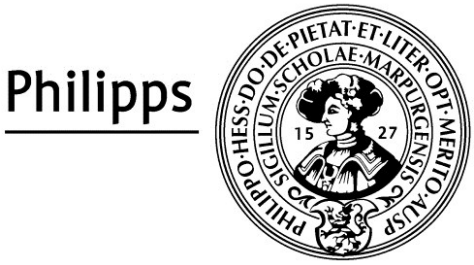

PLACEBOEFFEKTE IN DER PHARMAKOLOGISCHEN BEHANDLUNG VON INSOMNIE

Dissertation

zur Erlangung des Doktorgrades der Naturwissenschaften
(Dr. rer. nat.)

dem Fachbereich Psychologie der Philipps-Universität Marburg

vorgelegt von

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Marburg (Lahn), Februar 2016

Vom Fachbereich Psychologie der Philipps-Universität Marburg (Hochschulkennziffer 1080)
als Dissertation angenommen am 15.02.2016

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Tag der mündlichen Prüfung:	19.04.2016

Danksagung

(Die Danksagung ist nicht Teil der Veröffentlichung)

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1 Zusammenfassung und Abstract

1.1 Zusammenfassung

Placeboeffekten wird in neueren Studien ein substantieller Anteil an der Symptomverbesserung in der Pharmakotherapie zugesprochen. Im Bereich der pharmakologischen Behandlung von Insomnie gibt es bisher jedoch kaum Studien, die sich mit der Quantifizierung eines möglichen Placeboeffektes und der Untersuchung seiner zugrunde liegenden Wirkmechanismen befasst haben.

Die vorliegende Dissertation verfolgte daher zwei Ziele. Erstens wurde im Rahmen einer Metaanalyse die differentielle Wirksamkeit verschiedener Substanzklassen auf objektive und subjektive Zielgrößen in 31 randomisierten kontrollierten klinischen Studien (RCTs) zur pharmakologischen Behandlung von primärer Insomnie (3820 Patienten) erfasst (Studie 1). Hierbei wurden auch die Symptomverbesserungen innerhalb der Placebo-Kontrollgruppen der klinischen Primärstudien (32 RCTs mit 3969 Patienten) quantifiziert, sowie der Anteil des Placeboeffektes an der Symptomverbesserung in der Medikamentengruppe bestimmt (Studie 2). Dabei zeigte sich sowohl in subjektiven als auch in objektiven Zielgrößen bei einer eher moderaten Wirksamkeit über alle Substanzklassen hinweg, dass im Mittel 63.56% der Symptomverbesserung in der pharmakologischen Behandlung von Insomnie bereits in den Placebo-Kontrollgruppen erreicht wurde.

Zweitens wurde Konditionierung - als ein potentiell zugrunde liegender Wirkmechanismus des Placeboeffektes - im Rahmen eines Konditionierungsparadigmas an 39 gesunden Probanden untersucht (Studie 3). In der Machbarkeitsstudie konnte nicht, wie erwartet, demonstriert werden, dass sich in einer Akquisitionsphase gelernte pharmakologisch induzierte Veränderungen der Schlafarchitektur (Amitriptylin induzierte REM-Schlaf Suppression) in einer Evokationsphase durch die Einnahme eines Placebos wieder abrufen (imitieren) lassen. Vielmehr zeigte sich unerwartet ein signifikanter Effekt in die entgegengesetzte Richtung, also signifikant mehr REM-Schlaf in der Experimentalgruppe als in der Placebo-Kontrollgruppe. Die vorliegenden Befunde weisen darauf hin, dass einfache Regeln des assoziativen Lernens nicht ausreichen, um den beobachteten Placeboeffekt zu erklären. Es müssen komplexere Einflüsse, wie eine konditionierte Gegenreaktion oder eine homöostatische Gegenreaktion nach Absetzen der Studienmedikation (Rebound), die mit der Konditionierung interferierte, in Betracht gezogen werden.

1.2 Abstract

There is evidence that the placebo response accounts for a substantial proportion of symptom improvement in pharmacological treatments. Concerning insomnia drug trials, there is a lack of studies addressing the proportion of the placebo response on drug response and its underlying mechanisms.

Therefore this dissertation had two main purposes. First, to compare treatment efficacy of different drug classes addressing primary insomnia and their impact on subjective and objective outcomes by conducting a meta-analysis based on 31 randomized controlled trials (RCTs) including 3820 patients (study 1). Additionally symptom improvement in the placebo control condition was assessed for 32 RCTs including 3969 patients to compare its efficacy on objective versus subjective outcome measures, and to determine its proportion in the response to pharmacological treatments (study 2). Effect size estimates for the total sample of pooled drug classes suggest a small-to moderate effect for subjective as well as for objective outcomes. Our results indicate that 63.56% of the drug responses are achieved even in the placebo groups.

Second, since conditioning is supposed to be a potential mechanism of the placebo response we applied a paradigm of behavioral conditioning to 39 healthy participants using effects on sleep architecture as the objective outcome (study 3). In that proof of principle study we were unable to demonstrate that REM-sleep suppression triggered by amitriptyline is simply accessible to conditioning and could be evoked through a placebo pill intake in an evocation phase. Instead of the expected REM-sleep suppression in the evocation night, we observed more REM-sleep in the amitriptyline group. This result indicates that while simple conditioning does not seem to explain these effects, more complex influences (e.g. conditioning of the drug-antagonistic response or rebound) could be involved.

2 Hintergrund

2.1 Placebo

2.1.1 Definitionen und Begriffsklärung

Der Begriff *Placebo* stammt aus dem Lateinischen („ich werde gefallen“) und wird nach klassischer Definition üblicherweise verwendet, um eine Tablette ohne Wirkstoff zu beschreiben (die beispielsweise in klinischen Prüfungen eingesetzt wird um die Wirksamkeit eines Medikaments zu ermitteln). Neben der Einnahme einer solchen Scheinsubstanz gibt es weitere Formen von Scheinbehandlungen wie Scheinoperationen (Moseley et al., 2002) oder Placeboakupunktur (Enck, Klosterhalfen, & Zipfel, 2010), die auch als *Placebo* bezeichnet werden. Das klassische Konzept einer Placebo-Behandlung als unwirksame Behandlung hat sich in den letzten Jahren zu dem Konzept einer Simulation von aktiver Therapie innerhalb eines psychosozialen Kontextes gewandelt (Benedetti, 2014). Als entscheidend für die Wirksamkeit einer Placebo-Behandlung wird dabei das therapeutische Ritual (inklusive aller Kontextfaktoren wie Farbe einer Tablette, Arztkittel eines Behandlers, Praxissetting uvm.) angesehen und nicht die unwirksame Substanz als solche (Benedetti, 2014).

Ein Placeboeffekt ist im Allgemeinen die Reaktion, die auf eine Placebobehandlung erfolgt. Darüber hinaus ist das Auftreten von Placeboeffekten nicht auf Placebobehandlungen beschränkt. Auch im Rahmen jeder anderen Therapie können Placeboeffekte das Behandlungsergebnis entscheidend beeinflussen.

Unter Noceboeffekten werden diejenigen negativen Effekte einer Behandlung zusammengefasst, die nicht durch behandlungsspezifische Faktoren (z.B. spezifische pharmakologische Effekte), sondern unspezifische Effekte (z.B. Kontextfaktoren) hervorgerufen werden (Mora, Nestoriuc, & Rief, 2011). Hierbei kann sich der Noceboeffekt durch eine Symptomerzeugung, Symptomverschlimmerung oder durch die Verhinderung einer Symptomverbesserung äußern.

Die Begriffe Placeboeffekt und Placeboresponse (Placeboantwort) werden in der Literatur oft synonym verwendet. In manchen Publikationen wird der Placeboeffekt jedoch als jegliche Verbesserung des Gesundheitszustandes in einer Patientengruppe, die ein Placebo erhält, verstanden (eingeschlossen weiterer unspezifischer Faktoren wie Spontanremission, Regression zur Mitte, natürlicher Verlauf und die tatsächliche Placeboresponse). Die Placeboresponse wird dementsprechend als die tatsächliche neurobiologische und psychophysiologische Reaktion eines Individuums auf eine unwirksame Behandlung und damit als Teil des Placeboeffek-

tes verstanden (Enck et al., 2013; Schedlowski, Enck, Rief, & Bingel, 2015). In anderen Publikationen verhält es sich genau entgegengesetzt (Enck & Klosterhalfen, 2012; Kirsch, 2013). Zusammengefasst handelt es sich bei den inkonsistent verwendeten Begriffen Placeboeffekt und Placeboresponse um ein rein definitorisches Problem. Einigkeit besteht darin, dass die gemessene Symptomveränderung in einer Placebogruppe nicht durch eine Simulation einer aktiven Behandlung (und deren Kontextfaktoren) alleine, sondern durch viele weitere unspezifische Faktoren bedingt ist. Um den spezifischen Anteil der simulierten aktiven Behandlung an der gemessenen Symptomveränderung zu bestimmen, müssen dementsprechend andere unspezifische Faktoren abgezogen werden (Kirsch, 2013). Dies ist in der Praxis durch den Vergleich einer Placebogruppe mit einer Gruppe ohne Behandlung möglich. In dieser Arbeit werden dem Vorschlag Benedettis (2014) folgend die Begriffe Placeboeffekt und Placeboresponse synonym verwendet, um ein auf eine Placebo Behandlung folgendes psychobiologisches Phänomen in einem Individuum oder einer Gruppe zu beschreiben. Dieses psychobiologische Phänomen kann in einigen Fällen sowohl subjektiv (mit Hilfe von Fragebögen oder Interviews), als auch objektiv (mit Hilfe von physiologischen Messungen) erfasst werden.

2.1.2 Subjektives und objektives Assessment

Die Frage, ob sich Placeboeffekte gleichermaßen auf subjektiven Zielgrößen (z.B. durch Patientenfragebögen oder Interviews erhobene Daten) wie objektiven Zielgrößen (z.B. durch am Körper getragene Sensoren erhobene Daten) abbilden lassen, wird kontrovers diskutiert. Hierbei wird insbesondere angenommen, dass die subjektiven Zielgrößen einem Bias unterliegen (Benedetti, 2014). Hrobjartsson and Gøtzsche (2001) fanden in einer Metaanalyse über 130 Studien, die eine Placebobehandlung mit einer Bedingung ohne Behandlung verglichen, einen signifikanten Effekt über alle Studien, die subjektive Zielgrößen berichteten. Jedoch konnte ein solcher Effekt nicht über alle Studien, die objektive Zielgrößen berichteten demonstriert werden (Hrobjartsson & Gøtzsche, 2001). Gleichzeitig konnten in einigen Studien schon deutliche Placeboeffekte auf objektiven Zielgrößen nachgewiesen werden (Benedetti et al., 2003; Goebel et al., 2002; Wirth et al., 2011) . Der Zusammenhang von subjektiven und objektiven Veränderungen (also ob z.B. subjektive Veränderungen zu objektiven Veränderungen führen) ist in den letzten Jahren in den Hintergrund getreten und wurde durch die Frage nach neuronalen Substraten der subjektiven Veränderungen abgelöst (Benedetti, 2014). Vor diesem Hintergrund scheint es sinnvoll bei der Untersuchung der zugrunde liegenden Mechanismen der Placeboresponse nicht nur subjektive Zielgrößen sondern auch objektive Zielgrößen heran zu ziehen.

2.1.3 Wirkmechanismen der Placeboresponse

Als Hauptmechanismen der Placeboresponse werden die Erwartungen des Behandlungseffektes durch den Patienten, assoziative Lernprozesse (Konditionierung) sowie die Qualität der Beziehung zwischen Patient und Behandler angenommen (Schedlowski et al., 2015). Dabei scheinen Erwartungen vor allem dann eine tragende Rolle zu spielen, wenn bewusste Sinneswahrnehmungen (z.B. Schmerz) involviert sind, wohingegen klassische Konditionierung bei unbewussten physiologischen Funktionen im Mittelpunkt zu stehen scheint (Benedetti et al., 2003).

Mit Erwartungen sind dabei Annahmen gemeint, die eine Person über den Ausgang einer Behandlung hat. Diese können durch verbale Instruktion, vorangegangene Erfahrungen, soziale Einflüsse (Peergroup, Medien usw.) und individuelle biologische/genetische Unterschiede beeinflusst werden (Rief et al., 2015). Konditionierung beruht auf dem Prinzip der Kontingenz (dem Grad der Wahrscheinlichkeit des gemeinsamen Auftretens zweier Merkmale) von dargebotenen Ereignissen oder Stimuli. Wenn beispielsweise die Einnahme einer Kopfschmerztablette immer wieder mit einer Reduktion des Kopfschmerzes einhergeht, kann dies dazu führen, dass nach ausreichend häufiger Paarung die Einnahme einer optisch gleich gestalteten Tablette ohne Wirkstoff zur gleichen körperlichen Reaktion führt (Benedetti, 2014).

Der Anteil von Erwartungen und Konditionierung als verschiedene an der Placeboresponse beteiligte Mechanismen und deren Interaktion wird aktuell kontrovers diskutiert (Colloca, 2014; Kong & Benedetti, 2014; Pecina, Stohler, & Zubieta, 2014; Stewart-Williams & Podd, 2004). Colloca (2014) hat auf die Notwendigkeit hingewiesen, eine strikte Dichotomie zwischen beiden Wirkmechanismen zu vermeiden, da Konditionierung auch Informationsverarbeitung (z.B. bewusste oder unbewusste Erwartungen bezüglich eines zukünftigen Ereignisses) beinhaltet und umgekehrt Erwartungen oft mit unbewussten vorherigen Erfahrungen assoziiert sind. Rief et al. (2015) postulierten ein Modell zur Erklärung von Entwicklung, Persistenz und Veränderung von Erwartungen, in dem Konditionierungsprozessen eine tragende Rolle zugesprochen wird. Nach dem Modell resultieren Erwartungen daraus, dass spezifische Kontextfaktoren einer spezifischen Konsequenz vorhergehen (Rief et al., 2015). Stewart-Williams and Podd (2004) schlugen vor, Konditionierung als eine von diversen, in die Placeboresponse involvierten, Lernquellen (z.B. verbale Instruktion, Modellernen) zu betrachten, die in manchen, aber nicht allen Fällen, durch bewusste Erwartungen mediiert werden. Zusammenfassend erscheint es daher wenig sinnvoll eine strikte Dichotomie zwischen Erwartung und Konditionierung aufrecht zu erhalten.

2.2 Das additive Model in randomisierten kontrollierten Studien

Seit über 60 Jahren gelten doppel-blinde randomisierte Placebo-kontrollierte Studien (RCTs) als Standard-Untersuchungsdesign, um die Wirksamkeit neuer pharmakologischer Substanzen zu prüfen. Dabei werden Patienten randomisiert einer Verum Bedingung und einer Placebo-Bedingung zugeteilt und die Effekte in deren Zielgrößen kontrastiert. Hierdurch sollen spezifische Effekte der pharmakologischen Substanz (Verbesserung in der Verum-Bedingung) von unspezifischen Effekten der Behandlung (Verbesserung in der Placebo-Bedingung) getrennt werden. Dem RCT Untersuchungsdesign liegt dabei – wie in Abbildung 1 illustriert - die implizite Annahme eines additiven Modells zu Grunde (Kirsch, 2000), in dem sich der Effekt einer pharmakologischen Substanz durch die reine Differenz zwischen Verumeffekt und Placeboeffekt beschreiben lässt (Behandlungsergebnis = Verum-Effekt + Placebo-Effekt). Diese Annahme beinhaltet, dass in beiden Bedingungen (Verum und Placebo) die unspezifischen Effekte der Behandlung identisch sind, eine Annahme die zunehmend in Frage gestellt wird (Doering, Rief, & Petrie, 2014; Enck & Klosterhalfen, 2013). Ein Vorteil des additiven Models ist die Möglichkeit den Anteil des Placeboeffektes in der Pharmakotherapie zu bestimmen

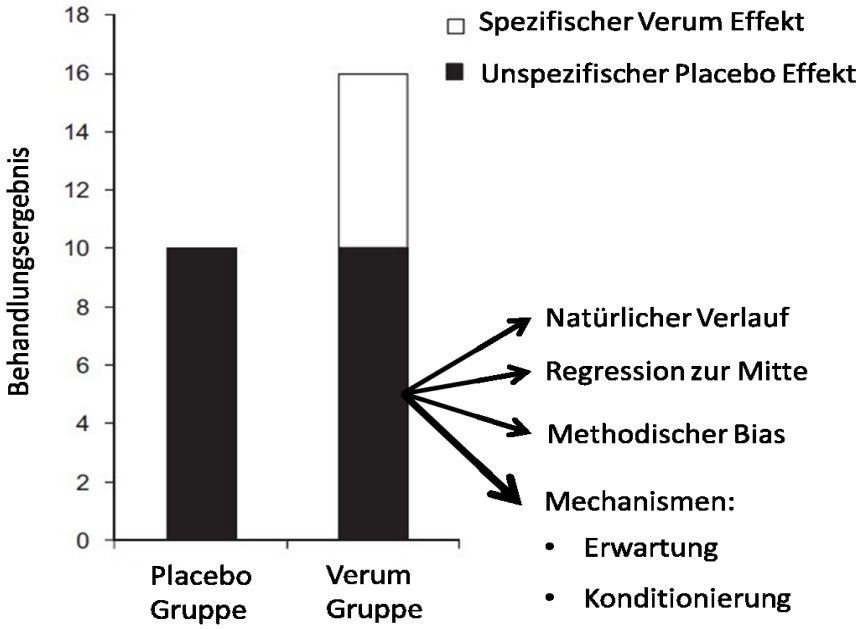

Abbildung 1: Das „additive Modell“ von randomisierten kontrollierten Studien (RCTs), das gleichgroße Placeboeffekte in beiden Studienarmen impliziert, die sich aus spontaner Symptomvariation, Regression zur Mitte und Kontextfaktoren (dem eigentlichen durch Wirkmechanismen erklärbaren Placeboeffekt) zusammensetzen (nach Enck et al., 2013).

2.3 Placebo Effekte in der Pharmakotherapie

Wiederholte pharmakologische Behandlungen werden zunehmend auch als „Lernprozess“ aufgefasst. Dies kann zum Beispiel bedeuten, dass der Körper auf eine neue Behandlung anders reagiert als auf die fünfte oder zehnte Wiederholung der Behandlung. Neben der bewussten Erwartungshaltung des Patienten scheinen dabei auch unbewusste Lern- oder Konditionierungsprozesse eine Rolle zu spielen (Stewart-Williams & Podd, 2004). In mehreren experimentellen Machbarkeits-Studien konnte die Konditionierbarkeit pharmakologischer Reaktionen am Beispiel von Veränderungen im Immunsystem (Goebel et al., 2002; Wirth et al., 2011), im endokrinen System (Benedetti et al., 2003) und bei respiratorischen Funktionen (Benedetti, Amanzio, Baldi, Casadio, & Maggi, 1999) gezeigt werden.

Wie in Abbildung 2 dargestellt, wird bei der Untersuchung von klassischer Konditionierung pharmakologischer Reaktionen üblicherweise ein pharmakologischer Wirkstoff (unkonditionierter Stimulus/US), der physiologische Veränderungen (unkonditionierte Reaktion/UR) hervorruft, mit einem neutralen Stimulus NS (z.B. Farbe und Form der Tablette oder einem neuartig schmeckenden Getränk) dargeboten. Nach mehrfacher Paarung beider Stimuli in einer Akquisitionsphase wird der zuvor neutrale Stimulus zu einem konditionierten Stimulus (CS). Die physiologischen Veränderungen, die ursprünglich durch den US ausgelöst wurden, können nun als konditionierte Response (CR) durch die Darbietung des CS alleine in einer Evokationsphase hervorgerufen werden (Enck et al., 2013).

Hierbei ist zu beachten, dass sich die Intensität, Dauer und die Wirklatenz von pharmakologischen Stimuli durch die Metabolisierung im Organismus im Vergleich zu sensorischen Stimuli unterscheiden (Flaten, 2009). Der US bei der Konditionierung von pharmakologischen Reaktionen ist streng genommen nicht die Substanz selbst, sondern der Effekt der pharmakologischen Substanz im zentralen Nervensystem (Eikelboom & Stewart, 1982; Ramsay & Woods, 1997). Die durch die Substanz hervorgerufenen physiologischen Veränderungen (UR) sind durch die Verteilung des Wirkstoffes im Organismus außerdem häufig vielfältig (Flaten, 2009). Ein kritischer Punkt im Konditionierungsprozess ist auch, dass im Prinzip jeder Stimulus im Kontext der Konditionierung (z.B. der Behandlungsraum, der weiße Kittel des Arztes u.v.m.) zum CS werden kann (Benedetti et al., 2003; Ramsay & Woods, 1997). Daher ist es wichtig bei der Wahl des gewünschten CS darauf zu achten, einen möglichst salienten Stimulus (z.B. auffälliges Aussehen der Tablette, ritualisierte Einnahme, außergewöhnlicher Geschmack) auszuwählen (Doering & Rief, 2012).

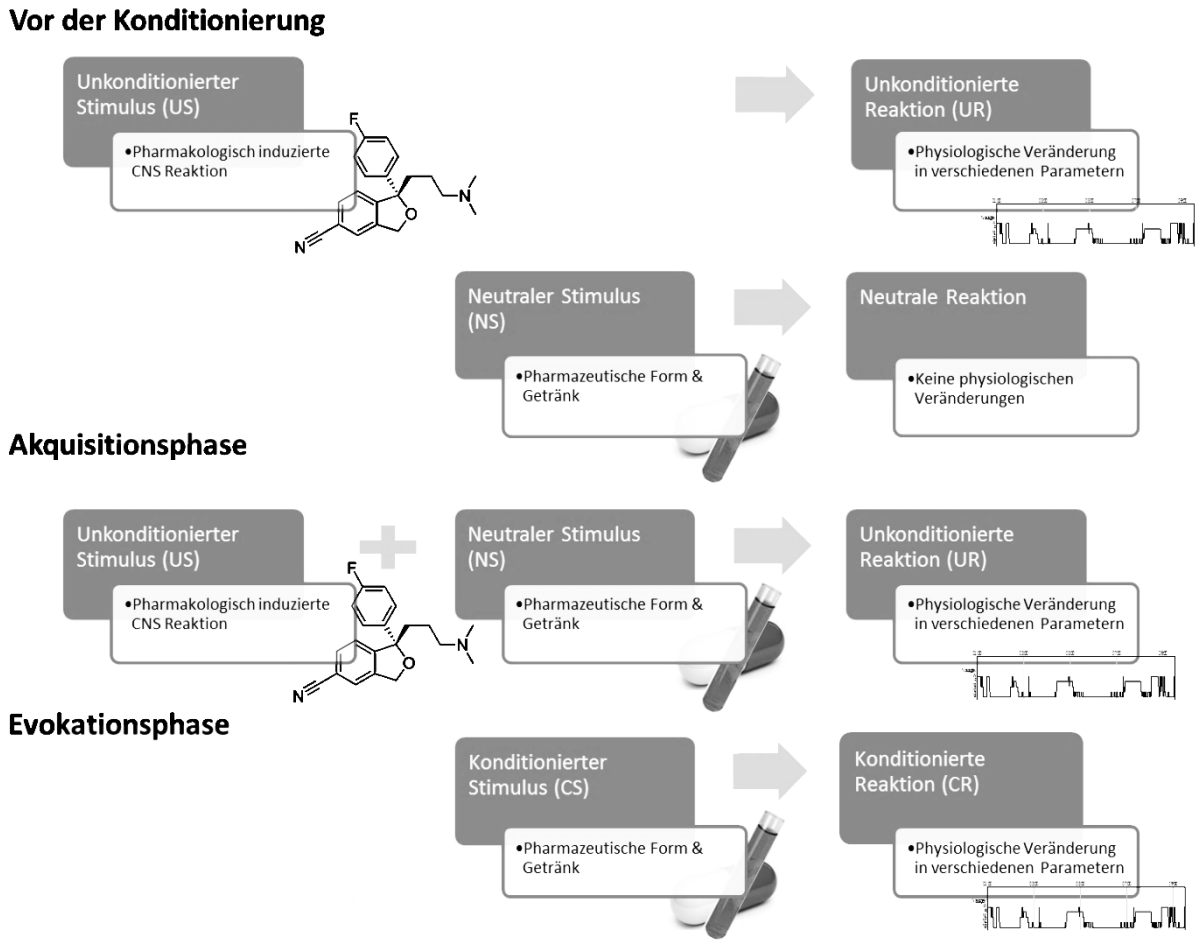

Abbildung 2: Konditionierungsparadigma mit pharmakologischen Stimuli (nach Doering & Rief, 2012). In der Akquisitionsphase wird ein pharmakologischer Wirkstoff, der eine Reaktion im zentralen Nervensystem (CNS) auslöst, mit einem neutralen Stimulus gepaart. In der Anschließenden Evokationsphase reicht die Darbietung des konditionierten Stimulus aus um eine konditionierte Reaktion hervorzurufen.

Wichtig ist auch, dass sowohl Substanz-agonistische als auch Substanz-antagonistische physiologische CR in der Literatur beschrieben werden. Es können durch den CS in der Evokationsphase also entweder die physiologischen Veränderungen durch den US imitiert oder eine homöostatische Gegenreaktion hervorgerufen werden (Flaten, 2009).

Perspektivisch kann die Konditionierung pharmakologischer Reaktionen bei der Methode der placebokontrollierten Dosisreduktion (PCDR) eine klinische Anwendung finden. Bei der PCDR wird ein Anteil einer Medikation sukzessive durch ein Placebo ersetzt, wobei die Wirksamkeit der Behandlung (bei Reduktion von Nebenwirkungen und Therapiekosten) aufrechterhalten werden kann (Doering & Rief, 2012). Die zugrunde liegenden Placebo-Mechanismen und ihre Implementierbarkeit in klinische Anwendungsfelder (z.B. durch PCDR) sind bisher jedoch unzureichend untersucht (Doering & Rief, 2012).

2.4 Schlaf

2.2.1 Die Physiologie des gesunden Schlafes

Schlaf ist ein reversibler Zustand komplexer physiologischer und behavioraler Prozesse, der subjektiv als Losgelöstsein von der eigenen Wahrnehmung und der Wahrnehmung der Umgebung erlebt wird (Kryger, Roth, & Dement, 2011). Die physiologischen Veränderungen während des Schlafes können mit Hilfe polysomnographischer Aufzeichnungen (PSG) – die ein Elektroenzephalogramm (EEG), Elektrookulogramm (EOG), Elektromyogramm (EMG), Elektrokardiogramm (EKG), Atemfluss, Atmungsanstrengung, Sauerstoffsättigung und Körperlage umfassen – aufgezeichnet werden. Das Manual zum Scoring von Schlaf und assoziierten Ereignissen der American Academy of Sleep Medicine (AASM-Manual; Iber, Ancoli-Israel, Chesson, & Quan, 2007) beschreibt die Aufnahme und die Regeln zur visuellen Auswertung der Polysomnographie. Die Schlafstadien lassen sich dabei in REM Schlaf (REM) und nicht-REM-Schlaf (NREM: N1, N2, N3) einteilen. Der Wachzustand ist durch Alpha-Aktivität im EEG, Anspannung der Muskulatur und schnelle Augenbewegungen gekennzeichnet. Schlafstadium N1 ist gekennzeichnet durch weniger Alpha-Aktivität und ein flacheres EEG im Theta-Frequenzbereich. Im Schlafstadium N2 treten K-Komplexe und Schlafspindeln im Beta-Frequenzbereich auf. Schlafstadium N3 bezeichnet man als Tiefschlaf (Slow Wave Sleep; SWS). N3 ist gekennzeichnet durch langsame Wellen hoher Amplitude im EEG, das Fehlen von Augenbewegungen und einem niedrigen Muskeltonus. REM Schlaf ähnelt im EEG N1, es besteht jedoch kein Muskeltonus und schnelle Augenbewegungen treten auf. Wesentliche und etablierte physiologische Schlaf-Parameter nach AASM (Iber et al., 2007) sind die im Bett verbrachte Zeit (TIB), Gesamtschlafzeit (TST), Einschlaflatenz (SOL), Wachperioden nach Schlafbeginn (WASO), Schlafeffizienz (SE; TST/TIB in %), Dauer und Anteil der einzelnen Schlafstadien an der Gesamtschlafdauer in Prozent.

Der gesunde Nachtschlaf von jungen Erwachsenen beginnt generell mit NREM-Schlaf. NREM und REM-Schlaf wechseln sich dann periodisch ca. alle 90 Minuten ab. SWS tritt überwiegend im ersten Drittel der Nacht auf. REM-Schlaf tritt überwiegend im letzten Drittel der Nacht auf. Der Wachzustand macht üblicherweise weniger als 5% der Nacht aus. N1 macht ca. 2-5%, N2 45-55% und N3 13-23% des Schlafes aus. Insgesamt besteht der Nachtschlaf daher aus 75-80% NREM-Schlaf und 20-25% REM-Schlaf, der in 4-6 separaten Episoden auftritt (Kryger et al., 2011). Im Falle einer Störung des Schlafes, wie bei dem Störungsbild der Insomnie, ist unter anderem der relative Anteil der beschriebenen Phasen pathologisch verändert.

2.2.2 Das Störungsbild der Insomnie

Insomnie ist eine weit verbreitete, häufig chronisch verlaufende Störung (Morin et al., 2009), die mit hohen direkten und indirekten Kosten in Verbindung gebracht wird (Daley, Morin, LeBlanc, Gregoire, & Savard, 2009). Sie ist charakterisiert durch Ein- und Durchschlafstörungen, frühmorgendliches Erwachen und die damit verbundenen Beeinträchtigungen der Befindlichkeit und der Leistungsfähigkeit. Sie betrifft ca. 10% der Bevölkerung in westlichen Industrienationen, wobei ein Drittel dieser chronischen Insomnien aufgrund fehlender ursächlicher Faktoren (körperliche Erkrankungen, psychische Störungen, Einnahme von Substanzen) als primäre Insomnien bezeichnet werden (Ohayon & Reynolds, 2009; Riemann, 2014). Abhängig von der Wahl des Diagnosesystems fanden Roth et al. (2011) im American Insomnia Survey Prävalenzraten zwischen 3,9% (Nicht-organische Insomnie nach ICD-10) und 22.1% (Primäre Insomnie nach DSM-IV-TR) für die Gesamtbevölkerung der USA.

Nach DSM-5 (American Psychiatric Association, 2013) steht bei der insomnischen Störung die Unzufriedenheit mit der Schlafqualität oder -quantität, verbunden mit einem (oder mehreren) der folgenden Symptome: (1) Schwierigkeiten einzuschlafen, (2) Schwierigkeiten durchzuschlafen, charakterisiert durch häufige Wachperioden oder Schwierigkeiten nach nächtlichen Wachperioden wieder einzuschlafen, (3) Frühmorgendliches Erwachen mit der Unfähigkeit wieder einzuschlafen, im Vordergrund. Die Schlafstörung führt zu klinisch signifikantem Leiden oder Einschränkungen im sozialen, ausbildungs- und beruflichen Leben oder anderen wichtigen Funktionsbereichen, tritt mindestens 3 Nächte pro Woche auf, hält mindestens 3 Monate an, tritt trotz ausreichender Gelegenheit für Schlaf ein und kann nicht besser durch eine andere Schlaf-Wach-Rhythmusstörung, koexistierende psychische oder körperliche Erkrankungen oder die physiologischen Effekte einer Substanz erklärt werden.

Die Differenzierung von Insomnie in primäre und sekundäre Insomnie wird im DSM-5 fallengelassen. Die insomnische Störung liegt nun als eigenständiges Krankheitsbild vor und kann auch bei komorbid vorliegenden körperlichen oder psychischen Erkrankungen vergeben werden, wenn diese die vorwiegend beklagten Schlafstörungen nicht adäquat erklären (American Psychiatric Association, 2013).

Zur Behandlung der Insomnie stehen neben verhaltenstherapeutischen Interventionen (Mitchell, Gehrman, Perlis, & Umscheid, 2012; Riemann, 2014) verschiedene pharmakologische Interventionen zur Verfügung (Smith et al., 2002).

2.2.3. Die Pharmakotherapie der Insomnie

In der ärztlichen Praxis wird Insomnie üblicherweise medikamentös mit Benzodiazepinen, Bezodiazepin-Rezeptor-Agonisten, Antihistaminika oder „off-label“ (also außerhalb der mit der Zulassung genehmigten Indikation) mit anderen sedierenden Substanzen (z.B. sedierende Antidepressiva) behandelt (Riemann, 2014). Dabei wird die empfohlene Behandlungsdauer von 2-4 Wochen häufig überschritten, was Fragen bezüglich Missbrauch, Toleranzentwicklung, Abhängigkeit und Nebenwirkungen aufwirft (Hoffmann, Pfannkuche, & Glaeske, 2008).

Trizyklische Antidepressiva werden laut Walsh and Schweitzer (1999) aufgrund ihres geringeren Abhängigkeitspotenzials zunehmend häufiger für die Behandlung von Insomnie verschrieben. Eine Metaanalyse zur Wirksamkeit von Antidepressiva in der Insomnie Behandlung von Buscemi et al. (2007) findet eine reduzierte Einschlaflatenz, weniger Wachphasen nach Schlafbeginn und eine verbesserte Schlafeffizienz und Gesamtschlafdauer im Vergleich zur Placebo-Kontrollgruppe. Ein häufiger Nebeneffekt der Einnahme eines trizyklischen Antidepressivums ist eine REM-Schlaf Reduktion, im Fall von Amitriptylin ist eine bis zu 50%ige Reduktion des REM-Schlafes gesunder Probanden sowie depressiver Patienten schon bei einer Dosis von 50mg zu beobachten (Doerr et al., 2010; Mayers & Baldwin, 2005; Winokur et al., 2001).

Es gibt erste Hinweise darauf, dass in der Pharmakotherapie von Schlafstörungen Placeboeffekte eine tragende Rolle spielen (Huedo-Medina, Kirsch, Middlemass, Klonizakis, & Siriwardena, 2012).

2.2.4. Placeboeffekte in der Pharmakotherapie der Insomnie

In klinischen Studien zur Wirksamkeit von pharmakologischer Therapie bei Schlafstörungen werden substanzielle Symptomverbesserungen auch in den Placebo-Kontrollgruppen berichtet (Belanger et al., 2007; Huedo-Medina et al., 2012; McCall, D'Agostino, & Dunn, 2003). In einer Studie zur Wirksamkeit von Benzodiazepin-Rezeptor-Agonisten von Huedo-Medina et al. (2012) zeigte sich, dass der Placeboeffekt fast der Hälfte des Medikamenteneffekts entsprach. Vor dem Hintergrund starker Placeboeffekte in der pharmakologischen Behandlung von Depressionen (Kirsch, 2014; Rief et al., 2009) erscheint es plausibel, dass auch bei dem Einsatz von Antidepressiva in der Insomnie-Behandlung Placeboeffekte eine große Rolle spielen könnten.

Erste empirische Ergebnisse sprechen dafür, dass subjektive wie objektive Schlafparameter durch Placebos veränderbar sind (Fratello et al., 2005). Neben der bewussten Erwartungshaltung des Probanden scheinen auch unbewusste Lern- oder Konditionierungsprozesse (klassische Konditionierung) eine Rolle bei der Wirkung von Placebos zu spielen (Stewart-Williams & Podd, 2004). In mehreren Studien konnte die Konditionierbarkeit von physiologischen Reaktionen (z.B. der Immunsuppression) durch pharmakologisches Konditionieren gezeigt werden (Goebel et al., 2002; Wirth et al., 2011).

Der substanzielle Anteil von Placeboeffekten am Medikamenteneffekt spricht vor dem Hintergrund der weiten Verbreitung von Insomnie und den Risiken und Nebenwirkungen einer pharmakologischen Behandlung dafür, die Placeboeffekte in der Pharmakotherapie der Insomnie weiter zu untersuchen, um perspektivisch eine evidenzbasierte klinische Nutzbarkeit dieser Placeboeffekte zu ermöglichen.

Ein Machbarkeitsnachweis für die Konditionierbarkeit von Veränderungen der Schlafarchitektur (z.B. der Amitriptylin induzierten REM-Schlaf-Suppression) steht trotz der starken Hinweise auf Placeboeffekte beim Einsatz von Amitriptylin bisher jedoch aus.

3 Darstellung des Dissertationsvorhabens

3.1 Relevanz und Herleitung der Fragestellungen

Seit Jahrzehnten sind Placeboeffekte als klinisch-relevante Phänomene bekannt. Neuere Studien weisen darauf hin, dass ein substantieller Anteil der Symptomverbesserung in der Pharmakotherapie auf Placeboeffekte zurückzuführen ist (Schedlowski et al., 2015). Die wissenschaftliche Untersuchung dieser behandlungsunspezifischen Effekte und deren Wirkmechanismen stecken trotz ihrer hohen therapeutischen Bedeutung noch in den Kinderschuhen. Perspektivisch könnte durch ein besseres Verständnis der zugrunde liegenden Mechanismen das Design klinischer Studien optimiert werden (Enck et al., 2013) und Placeboeffekte durch ihren systematischen Einsatz zu einer Steigerung der Wirksamkeit therapeutischer Interventionen und einer Reduktion von Nebenwirkungen sowie Therapiekosten beitragen (Doering & Rief, 2012).

Insomnie ist ein weit verbreiteter, häufig pharmakologisch behandelter Beschwerdekomplex (Leger, Poursain, Neubauer, & Uchiyama, 2008) und eignet sich daher gut, um die Bedeutung von Placeboeffekten und deren zugrunde liegende Mechanismen zu untersuchen. Außerdem bieten Schlafstörungen eine elegante Möglichkeit, Konditionierungsprozesse zu untersuchen, da Zielgrößen sowohl subjektiv als auch objektiv erfasst werden können, sich die Schlafarchitektur durch pharmakologische Wirkstoffe verändern lässt und Menschen keine bewussten Erwartungen bezüglich der ablaufenden neurophysiologischen Prozesse während des Schlafes haben.

Trotz signifikanter Risiken und Nebenwirkungen und einer unzureichenden Evidenzlage zur Wirksamkeit von Antidepressiva im Vergleich zu Benzodiazepinen und Benzodiazepin-Rezeptor Agonisten werden in der Praxis zunehmend Antidepressiva „off-label“ zur Behandlung von Insomnie eigensetzt (Walsh & Schweitzer, 1999). Die Wirksamkeit verschiedener Substanzklassen anhand objektiver wie subjektiver Kriterien zu evaluieren ist daher für die klinische Praxis hoch relevant. Des Weiteren gibt es erste Hinweise darauf, dass auch in der pharmakologischen Behandlung der Insomnie Placeboeffekte eine tragende Rolle spielen (Belanger et al., 2007; Huedo-Medina et al., 2012; McCall et al., 2003). Gerade vor dem Hintergrund eher moderater Behandlungseffekte und der substantiellen Risiken und Nebenwirkungen der pharmakologischen Behandlung primärer Insomnie, erscheint die Ermittlung des Anteils von Placeboeffekten am Gesamteffekt hoch relevant.

Das erste Ziel der Dissertation bestand daher darin, am Beispiel der pharmakologischen Behandlung von primärer Insomnie, die Wirksamkeit verschiedener Substanzklassen (Studie 1) und den Anteil der Symptomverbesserung, der auf Placeboeffekte zurückzuführen ist, zu bestimmen (Studie 2). In den entstandenen Übersichtsarbeiten zeigten sich kleine bis moderate Effektstärken über alle Substanzklassen hinweg. Placeboeffekte konnten sowohl in subjektiven als auch in objektiven Zielvariablen erfasst werden. Der mittlere Anteil des Placeboeffektes an der Symptomverbesserung lag bei 63,56%, was darauf hinweist, dass ein großer Anteil des therapeutischen Effektes durch die Optimierung von Placebo-Mechanismen erreicht werden kann. Für diese Optimierung ist ein breiteres Wissen über die zugrunde liegenden Mechanismen erforderlich.

Daher war ein weiteres Ziel der Dissertation, die zugrundeliegenden Mechanismen des in Studie 2 gefundenen Placeboeffektes in der pharmakologischen Behandlung von primärer Insomnie zu explorieren (Studie 3). Konditionierung wird als ein Schlüssel-Mechanismus der Placeboresponse, insbesondere in physiologischen Prozessen, angenommen (Frisaldi, Piedimonte, & Benedetti, 2015; Schedlowski & Pacheco-López, 2010) und schon erfolgreich am Beispiel anderer physiologischer Systeme untersucht (Benedetti et al., 2003; Goebel et al., 2002). Daher versuchten wir in einem experimentellen Konditionierungsparadigma die Konditionierbarkeit von pharmakologisch induzierten Veränderungen der Schlafarchitektur an gesunden Probanden zu demonstrieren. Dies ist ein wichtiger erster Schritt, um die Rolle von Konditionierungsprozessen in der pharmakologischen Behandlung von Patienten mit primärer Insomnie zu untersuchen.

3.2 Fragestellungen des Dissertationsvorhabens

Basierend auf der bisherigen Forschungslage wurden – wie in Abbildung 3 illustriert - dem Dissertationsvorhaben folgende Fragestellungen zu Grunde gelegt:

Studie 1: Wie wirksam ist die pharmakologische Behandlung der primären Insomnie? Unterscheiden sich verschiedene Substanzklassen zur pharmakologischen Behandlung von primärer Insomnie in ihrer Wirksamkeit? Zeigen sich die Symptomverbesserungen gleichermaßen in objektiven und subjektiven Zielgrößen?

Studie 2: Wie groß sind die Effekte einer Placebobehandlung von primärer Insomnie? Zeigen sich die Symptomverbesserungen gleichermaßen in objektiven und subjektiven Zielgrößen? Wie groß ist der Anteil der Symptomverbesserung in den Verum-Gruppen, der auf Placeboeffekte zurückzuführen ist?

Studie 3: Ist es möglich pharmakologisch induzierte Veränderungen der Schlafarchitektur (am Beispiel des REM-Schlaf unterdrückenden Effektes von Amitriptylin) im Rahmen eines klassischen Konditionierungsparadigmas zu lernen und mit Hilfe eines Placebos wieder abzurufen?

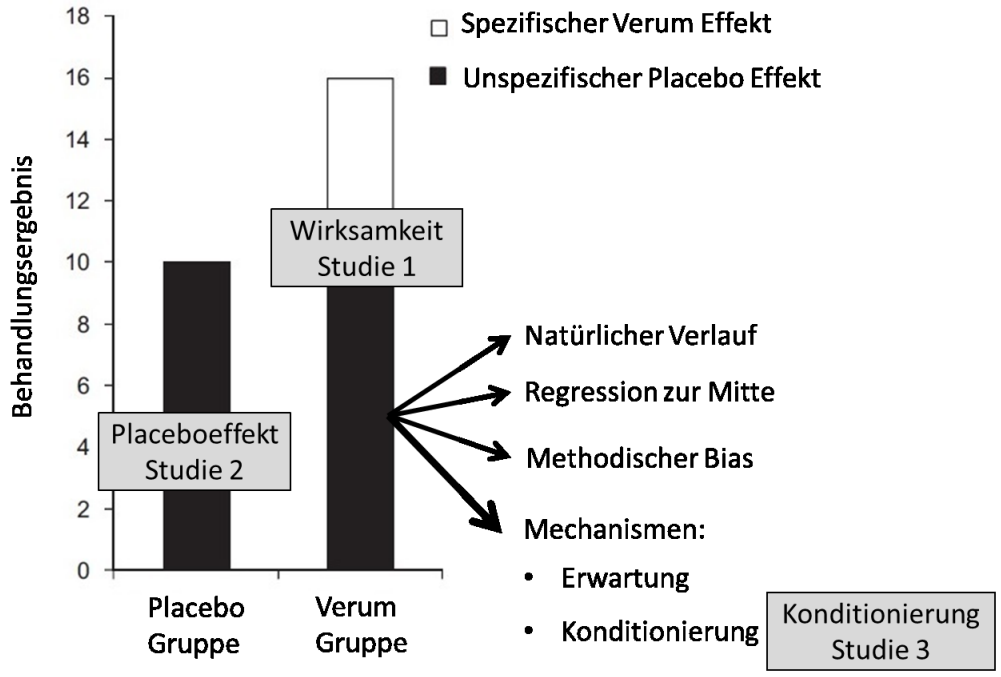

Abbildung 3: Fragestellungen der Dissertation im Kontext des „additiven Modells“ von RCTs

Im Folgenden werden die drei Studien zusammenfassend dargestellt.

4 Zusammenfassung der Studien

4.1 Studie 1: Die Wirksamkeit der pharmakologischen Insomnie-Behandlung

Zitation: Winkler, A., Auer, C., Doering, B., & Rief, W. (2014). Drug Treatment of Primary Insomnia: A Meta-Analysis of Polysomnographic Randomized Controlled Trials. CNS Drugs, 28(9), 799-816. doi: 10.1007/s40263-014-0198-7

Hintergrund. Bei primärer Insomnie handelt es sich um einen weit verbreiteten und häufig pharmakologisch behandelten Beschwerdekomplex, der durch Einschlafschwierigkeiten, Durchschlafschwierigkeiten oder Früherwachen charakterisiert ist. Im American Insomnia Survey zeigten sich Prävalenzraten von 3.9% bei Verwendung der ICD-10 Kriterien und 22.1% bei Verwendung der DSM-IV-TR Kriterien (Roth et al., 2011). Nur etwas weniger als die Hälfte der Betroffenen konsultieren einen Arzt aufgrund ihrer Beschwerden. Die Mehrheit derjenigen, die einen Arzt konsultieren, erhalten dann eine pharmakologische Behandlung (Leger et al., 2008). Diese besteht oft aus klassischen Benzodiazepinen (BDZ), Benzodiazepin-Rezeptor-Agonisten (BZRA) oder einer Off-Label-Behandlung mit Antidepressiva (ADP) (Buscemi et al., 2007). Die Unterschiede in der Wirksamkeit verschiedener Substanzklassen auf Grundlage objektiver (polysomnographischer) Daten sind bisher jedoch unzureichend untersucht. Auch Unterschiede zwischen subjektiven Zielgrößen und objektiven Zielgrößen in Bezug auf die Wirksamkeit verschiedener Substanzklassen sind unzureichend untersucht.

Methode. Um die Wirksamkeit verschiedener Substanzklassen bezüglich der jeweils objektiv (per Polysomnographie) und subjektiv (per Schlaftagebuch) erfassten Zielgrößen „Total Sleep Time“ (TST, sTST), “Sleep Onset Latency” (SOL, sSOL), “Wake After Sleep Onset” (WASO, sWASO) und “Sleep Efficiency” (SE, sSE) miteinander zu vergleichen, wurden in einer umfangreichen Suche in PsycINFO, PSYNDEX, PubMed, PQDT OPEN, OpenGREY, ISI Web of Knowledge, Cochrane Clinical Trials und der WHO International Clinical Trials Registry Platform 420 Studien identifiziert. Von den identifizierten Studien konnten 31 randomisierte kontrollierte klinische Studien zur pharmakologischen Behandlung von primärer Insomnie (3820 Teilnehmer), die ausreichend (polysomnographische) Daten berichteten, um Effektstärken zu berechnen, eingeschlossen werden. Kontrollierte Effektstärken (Hedge’s g) wurden berechnet und mithilfe eines Random-Effects-Modells integriert. Verschiedene Substanzklassen (BDZ, BZRA und ADP) wurden dabei in Subgruppenanalysen miteinander verglichen.

Ergebnisse. Die Effektstärken für die mittlere Wirksamkeit aller Substanzklassen zusammengefasst weisen auf kleine bis moderate, jedoch signifikante und robuste Effekte für objektive Zielgrößen (TST g = 0.27, SOL g = -0.36, WASO g = -0.29, SE g = 0.29) sowie subjektive Zielgrößen (sTST g = 0.21, sSOL g = -0.24, sWASO g = -0.21, sSE g = 0.41) hin. Die Ergebnisse liefern darüber hinaus einen Hinweis darauf, dass BZRA und BDZ wirksamer die Einschlaflatenz verkürzen als ADP und dass BDZ den BZRA bezüglich der Verkürzung der subjektiven Einschlaflatenz überlegen sind. In der Subgruppe der BZRA zeigte sich außerdem, dass die Effektstärken für objektive Zielgrößen (TST, SOL) signifikant größer waren als für subjektive Zielgrößen (sTST, sSOL). Moderator-Analysen zeigen, dass qualitativ hochwertigere Studien und Studien, die eine ältere Stichprobe untersuchten, leicht höhere Effektstärken berichteten.

Diskussion. Der Befund, dass die Effekte der pharmakologischen Therapie von primärer Insomnie insgesamt eher moderat sind, steht im Einklang mit der bestehenden Literatur (Buysse, 2013; Huedo-Medina et al., 2012). Die pharmakologische Therapie scheint daher gegenüber der Placebo-Kontrollgruppe nur leicht überlegen zu sein. Folgende wichtige Einschränkungen der aktuellen Studie sollten berücksichtigt werden. Trotz einer umfangreichen Suche nach unpublizierten Studien konnten wir keine unpublizierten Daten in unsere Analyse einschließen, was zu einem publication bias und damit zu einer Überschätzung der gefundenen Wirksamkeit der pharmakologischen Insomnie-Behandlung geführt haben könnte. Des Weiteren haben wir zur Quantifizierung der Wirksamkeit Effektstärken berechnet und auf statistische Signifikanz geprüft. Es bleibt jedoch unklar, ob ein statistisch signifikanter Effekt einem klinisch signifikanten Effekt (also einer signifikanten Verbesserung der Beschwerden eines Insomnie-Patienten) entspricht. Daten über das Nebenwirkungsprofil und Sicherheitsaspekte der Substanzklassen wurden nicht mitanalysiert, was eine vollständige Kosten-Nutzen-Analyse verhindert, da der klinische Nutzen eines Medikaments nicht nur von seiner Wirksamkeit, sondern auch von seinem Nebenwirkungsprofil abhängt. Zukünftige Studien sollten sowohl objektive als auch subjektive Erhebungsmethoden nutzen, um die Wirksamkeit von pharmakologischen Therapien bei primärer Insomnie umfassend abbilden zu können. Bezüglich der Wirksamkeit sollten Praktiker BZRA und BDZ gegenüber ADP bevorzugen. Allerdings sollten Aspekte der Medikamentensicherheit sowie die unterschiedlichen Nebenwirkungsprofile in die Auswahl einer Substanzklasse zur Therapie von Insomnie Patienten mit einfließen.

4.2 Studie 2: Placeboeffekte in der pharmakologischen Insomnie-Behandlung

Zitation: Winkler, A., & Rief, W. (2015). Effect of Placebo Conditions on Polysomnographic Parameters in Primary Insomnia: A Meta-Analysis. Sleep, 38(6), 925-931. doi: 10.5665/sleep.4742

Hintergrund. Randomisierte kontrollierte Studien (RCTs), die die Wirksamkeit einer pharmakologischen Behandlung der primäreren Insomnie – einem durch Einschlafschwierigkeiten, Durchschlafschwierigkeiten oder Früherwachen charakterisierten Beschwerdekomplex – untersuchen, verwenden häufig Placebo-Vergleichsgruppen. Bisherige Metaanalysen weisen auf einen substanziellen Effekt einer Placebo-Tabletten-Einnahme in diesen Vergleichsgruppen auf subjektive Zielgrößen der primären Insomnie hin. Dennoch ist die Wirksamkeit einer Placebo-Behandlung auf Grundlage objektiver, d.h. polysomnographischer (PSG) Daten, bisher unzureichend untersucht.

Methode. Um die Wirksamkeit einer Placebo-Behandlung bei primärer Insomnie auf Grundlage objektiver (PSG) Daten zu untersuchen und mit der Wirksamkeit einer pharmakologischen Behandlung zu vergleichen, wurden nach einer umfangreichen Literatursuche in PsycINFO, PSYNDEX, PubMed, PQDT OPEN, OpenGREY, ISI Web of Knowledge, Cochrane Clinical Trials und der WHO International Clinical Trials Registry Platform 32 polysomnographische RCTs (insgesamt 82 Behandlungsbedingungen mit N = 3969 Patienten) in die quantitative Analyse eingeschlossen. Prä-Post Effektstärken (Hedge's g) wurden für Placebo-Gruppen und Verum-Gruppen getrennt berechnet und jeweils mit Hilfe eines Random-Effects-Modells integriert. Anschließend wurden die mittleren Effektstärken der Placebo-Gruppen von den mittleren Effektstärken der Verum-Gruppen abgezogen um den Anteil der Placeboresponse an der Medikamenten-Response zu ermitteln. Außerdem wurden subjektive Zielgrößen und objektive Zielgrößen miteinander verglichen.

Ergebnis. Die Effektstärken (Hedge's g) weisen auf kleine bis mittlere, signifikante und robuste Effekte einer Placebo-Behandlung bezüglich der objektiven Zielvariablen Einschlaflatenz (−0.35), Gesamtschlafdauer (0.42), Wachzeit nach Schlafbeginn (−0.29), Schlafeffizienz (0.31), sowie der subjektiven Zielvariablen subjektive Einschlaflatenz (−0.29), subjektive Gesamtschlafdauer (0.43), subjektive Wachzeit nach Schlafbeginn (−0.32), subjektive Schlafeffizienz (0.25) und subjektive Schlafqualität (0.31) hin. Hierbei konnte kein signifikanter Unterschied zwischen objektiven und subjektiven Zielvariablen gefunden werden. Außerdem liefern die Ergebnisse einen Hinweis darauf, dass gemittelt 63,56% des Behandlungs-

effektes von pharmakologischen Interventionen auf die Placeboresponse zurückzuführen sind. Der Anteil der Placeboresponse variiert dabei zwischen den Zielvariablen Einschlaflatenz (64%), Gesamtschlafdauer (53%), Wachzeit nach Schlafbeginn (53%), Schlafeffizienz (48%), subjektive Einschlaflatenz (64%), subjektive Gesamtschlafdauer (80%), subjektive Wachzeit nach Schlafbeginn (100%), subjektive Schlafeffizienz (39%) und subjektive Schlafqualität (61%) erheblich.

Diskussion. Aufgrund methodischer Limitationen, wie der Berechnung von Prä-Post-Effektstärken innerhalb der Gruppen (aus Ermangelung von Studien, die eine Wartegruppe und eine Placebogruppe in einem Trial berichten), sowie dem Subtrahieren von den Effektstärken der Placebo-Kontrollgruppen von den Effektstärken der Verum-Gruppen (basierend auf dem additiven Modell), können die berichteten Ergebnisse nur als vorläufige Ergebnisse interpretiert werden. Dennoch sollten (vor dem Hintergrund substanzieller Risiken und Nebenwirkungen in der pharmakologischen Behandlung von primärer Insomnie und dem hohen Anteil der Placeboresponse an deren Wirksamkeit) zukünftige Studien Placebo-Mechanismen sowie deren Implementierbarkeit in klinische Anwendungsfelder untersuchen, um die gefundenen signifikanten Effekte einer Placebo-Behandlung von primärer Insomnie in der Praxis nutzbar zu machen.

4.3 Studie 3: Konditionierbarkeit von Veränderungen der Schlafarchitektur

Zitation: Winkler, A., Rheker, J., Doering, B., & Rief, W. (submitted). Conditioning of Amitriptyline-Induced REM-Sleep Suppression in Healthy Participants: A Randomized Controlled Trial. Manuscript submitted for publication

Hintergrund. In klinischen Studien zur Wirksamkeit von pharmakologischer Therapie bei Schlafstörungen werden substanzielle Symptomverbesserungen auch in den Placebo-Kontrollgruppen berichtet. Assoziatives Lernen (Konditionierung) ist einer der angenommenen Wirkmechanismen dieser Placeboresponse. Zwar konnte die Konditionierbarkeit von pharmakologischen Reaktionen schon am Beispiel von Veränderungen im Immunsystem, Hormonsystem oder im respiratorischen System gezeigt werden, ein Machbarkeitsnachweis für die Konditionierbarkeit von pharmakologischen Veränderungen der Schlafarchitektur steht bisher jedoch aus.

Methode. Um den Machbarkeitsnachweis zu erbringen, haben wir ein Konditionierungsparadigma bei 39 gesunden Erwachsenen angewendet, die randomisiert und doppelblind zwei

Gruppen zugeordnet wurden (Experimentalgruppe und Kontrollgruppe). Probanden der Experimentalgruppe nahmen ein neuartig schmeckendes Getränk (100ml blau gefärbter Lycheesaft mit Waldmeister-Sirup) als neutralen Stimulus (NS) zusammen mit einem REM-Schlaf unterdrückendem trizyklischen Antidepressivum (50 mg Amitriptylin pro Tablette) als unkonditionierten Stimulus (US) in einer viertägigen Akquisitionsphase jeweils 30 Minuten vor dem Zubettgehen ein. Der Schlaf wurde zur Baseline und in der dritten Nacht der Akquisitionsphase mittels ambulanter Polysomnographie erfasst. Zielgröße war der prozentuale Anteil von REM-Schlaf an der Gesamtschlafdauer. Nach einer drei- bis viertägigen Auswaschphase, in der keine Tabletten mehr eingenommen wurden, folgte eine Evokationsnacht, in der Probanden der Experimentalgruppe erneut das Getränk (jetzt konditionierter Stimulus, CS) diesmal zusammen mit einer Placebotablette ohne Wirkstoff bekamen. Wieder wurde der Schlaf polysomnographisch erfasst. Probanden der Placebo-Kontrollgruppe durchliefen den gleichen Versuchsaufbau mit dem Unterschied, dass sie auch während der Akquisitionsphase Placebotabletten ohne Wirkstoff, anstatt Amitriptylin, einnahmen.

Ergebnis. Die Gruppen unterschieden sich zur Baseline nicht hinsichtlich des prozentualen Anteils von REM-Schlaf an der Gesamtschlafdauer. Es zeigte sich ein signifikanter Gruppenunterschied in der Akquisitions- und der Evokationsnacht, wie durch die signifikante Interaktion zwischen den Faktoren Zeit (Baseline, Akquisitionsphase, Evokationsphase) x Gruppe (Amitriptylin oder Placebo) einer Messwiederholungs-Varianzanalyse (ANOVA) demonstriert werden konnte ($F(2, 32) = 32.92$, $p < .001$). Erwartungsgemäß wurde im Vergleich zur Placebo-Gruppe reduzierter REM-Schlaf in der Experimentalgruppe am Ende der Akquisitionsphase gemessen. Anstelle des erwarteten imitierten unterdrückten REM-Schlafs in der Evokationsnacht zeigte sich jedoch signifikant mehr REM-Schlaf in der Experimentalgruppe als in der Placebo-Kontrollgruppe, wie jeweils durch Bonferroni-korrigierte paarweise Vergleiche statistisch gezeigt werden konnte.

Diskussion. Als mögliche Erklärungen für den Befund, dass sich in der Evokationsnacht signifikant mehr REM-Schlaf in der Experimentalgruppe zeigte, kommen eine konditionierte Gegenreaktion oder eine homöostatische Gegenreaktion nach Absetzen der Studienmedikation (Rebound) in Frage. Wir waren nicht in der Lage zu zeigen, dass die durch Amitriptylin ausgelöste REM-Schlaf Suppression einfachen Regeln des assoziativen Lernens unterliegt. Es ist davon auszugehen, dass komplexere Einflüsse involviert sind.

5 Zusammenfassende Diskussion und Ausblick

In der vorliegenden Dissertation ist es gelungen, einen metaanalytischen Überblick über verschiedene, in der pharmakologischen Therapie von Insomnie eingesetzte, Substanzklassen und deren differentieller Wirksamkeit bezüglich Symptomverbesserungen auf objektiven und subjektiven Zielvariablen zu geben (Studie 1). Hierbei zeigten sich sowohl für subjektive als auch objektive Zielgrößen insgesamt kleine bis moderate Effekte über alle Substanzklassen hinweg. Benzodiazepin-Rezeptor Agonisten und klassische Benzodiazepine zeigten sich als signifikant wirksamer in der Reduktion der Einschlaflatenz als Antidepressiva. Bezüglich der Einschlaflatenz und der Gesamtschlafdauer zeigten Benzodiazepin-Rezeptor Agonisten in objektiven Zielgrößen größere Effekte als in subjektiven Zielgrößen.

In einer anschließenden Analyse der Veränderungen in den Placebo Kontrollgruppen der eingeschlossenen Primärstudien zeigten sich ebenfalls kleine bis moderate Effekte in objektiven wie subjektiven Zielgrößen (Studie 2). Hierbei konnte gezeigt werden, dass im Mittel 63.56% der Symptomverbesserung in der pharmakologischen Behandlung von Insomnie bereits in den Placebo-Kontrollgruppen erreicht wurde.

Darauffolgend wurde in einer Machbarkeitsstudie erstmalig ein klassisches Konditionierungsparadigma auf die Veränderung der Schlafarchitektur gesunder Probanden angewandt, um zu untersuchen, ob im Bereich der pharmakologischen Behandlung von Insomnie Konditionierung als zugrunde liegender Mechanismus der Placeboresponse in Frage kommt. Hierbei ergaben sich Hinweise darauf, dass eine Amitriptylin induzierte REM-Schlaf Suppression nicht durch einfache Konditionierung gelernt und durch eine Placebo-Tablette abgerufen werden kann, sondern dass komplexere Prozesse wie eine konditionierte Wirkstoff-antagonistische Reaktion oder ein mit der Konditionierung interferierender Rebound berücksichtigt werden müssen. Auf Grundlage unserer Befunde ist es demnach nicht möglich, abschließend zu beantworten, ob pharmakologisch induzierte Veränderungen der Schlafarchitektur im Rahmen eines klassischen Konditionierungsparadigmas gelernt werden können.

5.1 Einschränkungen

Die Ergebnisse der ersten beiden Studien sind mit den für Metaanalysen üblichen Einschränkungen zu interpretieren. Um einem Publikations-Bias entgegenzuwirken, wurde eine umfangreiche Literatursuche inklusive mehrerer Strategien zum Auffinden von unpublizierten Studien durchgeführt. Dennoch kann ein potentieller Einfluss eines Publikations-Bias nicht

vollständig ausgeschlossen werden. Außerdem wurde bei der Integration nicht systematisch zwischen guten und schlechten Arbeiten unterschieden (*garbage in – garbage out*). Die Qualität der Studien wurde jedoch jeweils erfasst und als Moderator berücksichtigt. Außerdem wurden die Einschlusskriterien so gewählt, dass der Einschluss von qualitativ schlechten Studien unwahrscheinlicher wurde. Eine weitere Einschränkung stellt auch die Interpretation statistisch signifikanter Effektstärken ohne Berücksichtigung der klinischen Signifikanz dar. Zwar wurden sowohl objektive als auch subjektive Zielgrößen ausgewertet, ab wann jedoch ein statistisch signifikanter Gruppenunterschied in einer subjektiven oder objektiven Zielgröße auch eine klinische Signifikanz besitzt, war nicht Gegenstand der Untersuchung. Darüber hinaus wurden in den Metaanalysen keine Daten zur Medikamentensicherheit analysiert, was eine vollständige Risiko-Nutzen Analyse erschwert. Kliniker sollten neben der Wirksamkeit verschiedener Substanzklassen immer das Nebenwirkungsprofil, Abhängigkeitspotenzial und mögliche Rebound-Effekte in die Behandlungsentscheidung einfließen lassen.

In Studie 2 ist zu beachten, dass bei der Analyse von Prä-Post-Effektstärken innerhalb der Gruppen ein potentieller Einfluss durch unkontrollierte Faktoren (wie den natürlichen Verlauf der Erkrankung oder Regression zur Mitte) nicht ausgeschlossen werden kann, auch wenn im Fall der primären Insomnie eher von einer Chronifizierung als von einer Spontanremission ausgegangen werden kann (Morin et al., 2009). Des Weiteren beruht unser Vorgehen zur Ermittlung des Anteils der Placeboresponse an der Symptomverbesserung in der Medikamentengruppe auf den Annahmen des additiven Modells, dass in der Literatur zunehmend in Frage gestellt wird (Doering et al., 2014; Enck et al., 2013).

Da es sich bei Studie 3 um eine erste Machbarkeitsstudie handelt, ist grundsätzlich fraglich, ob Konditionierungsparadigmen aus der Neuroendokrinologie oder Immunologie auf die Modulation der Schlafarchitektur angewendet werden können. Im Speziellen ist unklar, ob die Anzahl an Akquisitionsnächten, Evokationsnächten und die Dauer der Auswaschphase (angelehnt an die oben genannten Paradigmen) für eine Konditionierung der REM-Schlaf-Suppression richtig bemessen waren. Durch das zeitlich verzögerte Einsetzen der REM-Schlaf-Suppression 90-120 Minuten nach Einnahme des neuartig schmeckenden Getränks zusammen mit der Tablette, stellt sich außerdem die Frage, ob das Getränk, wie intendiert, zum konditionierten Stimulus (CS) wurde. Möglich wäre auch, dass trotz des auffälligen Aussehens und des außergewöhnlichen Geschmacks ein anderer – nicht kontrollierter – Stimulus im Kontext der Konditionierung zum CS wurde. Des Weiteren ist eine Generalisierung der

Befunde aus Studie 3 auf gesunde Probanden beschränkt. Auch eine differenzierte Analyse von Respondern und Nonrespondern war auf Grundlage unserer Daten nicht möglich.

5.3 Perspektiven

Ausgehend von der vorliegenden Arbeit lassen sich mehrere Implikationen für weitere Forschung ableiten. Klinische Prüfungen sollten in Zukunft möglichst stets sowohl objektive als auch subjektive Daten erfassen, um ein vollständiges Bild über die physiologische sowie die Wahrnehmungskomponente von Insomnie zu liefern. Außerdem sollten immer systematisch Daten zur Medikamentensicherheit berichtet werden, um Praktikern eine fundierte Risiko-Nutzen-Einschätzung zu erleichtern. Darüber hinaus sollten sowohl Placebo-Kontrollgruppen als auch Wartelisten-Kontrollgruppen in das Studiendesign integriert werden, um den eigentlichen Anteil des Placeboeffektes noch genauer vom natürlichen Krankheitsverlauf und statistischen Phänomenen wie der Regression zur Mitte abgrenzen zu können. Zukünftige Metaanalysen zur pharmakologischen Therapie von primärer Insomnie sollten zusätzlich Daten zur Medikamentensicherheit und Nebenwirkungsprofilen berücksichtigen, um eine vollständige und nach Substanzklassen differenzierte Risiko-Nutzen –Analyse zu ermöglichen.

Zukünftige Studien zu Placebo-Mechanismen sollten einen Weg finden, den Anteil der Placeboresponse an der Symptomverbesserung in der Medikamentengruppe unabhängig vom additiven Modell zu bestimmen, da die impliziten Annahmen des Modells zunehmend in Frage gestellt werden (Enck et al., 2013). Um einen deutlichen Hinweis auf die Konditionierbarkeit von Veränderungen der Schlafarchitektur zu erbringen, sollten zukünftige Studien die Stimuli, Anzahl der Akquisitionsnächte und Evokationsnächte sowie die Dauer der Auswaschphase systematisch variieren. Perspektivisch sollten die so gewonnenen Erkenntnisse über Konditionierung als Mechanismus der Placeboresponse an klinischen Stichproben (z.B. Patienten mit primärer Insomnie) repliziert werden, um der Implementierbarkeit in die klinische Praxis näher zu kommen. Auch sollten zukünftige Studien psychologische, physiologische und neurobiologische Prädiktoren der Placeboresponse untersuchen, um Responder und Nonresponder besser differenzieren zu können.

Des Weiteren sollte (vor dem Hintergrund unserer Befunde zur Rolle des Placeboeffektes in der pharmakologischen Behandlung von Insomnie) genauer untersucht werden, wie die substantiellen Placeboeffekte in der klinischen Praxis der Insomnie-Behandlung systematisch nutzbar gemacht bzw. optimiert werden können.

5.4 Implikationen für die klinische Praxis

Unsere Ergebnisse sprechen dafür, im Fall einer pharmakologischen Intervention zur Reduktion der Einschlaflatenz (z.B. bei vom Patienten berichteten Einschlafstörungen) Benzodiazepin-Rezeptor Agonisten oder klassische Benzodiazepine statt „off-label“ Antidepressiva einzusetzen, wenn die vom Kliniker vorzunehmende Risikoeinschätzung es zulässt. Vor dem Hintergrund der gefundenen, eher moderaten Wirksamkeit und bedeutsamer Risiken und Nebenwirkungen pharmakologischer Interventionen bei primärer Insomnie sollten Kliniker auch kognitive Verhaltenstherapie als evidenzbasierte Behandlungsoption (Mitchell et al., 2012) in Betracht ziehen.

Auf Grundlage unserer Befunde zu Konditionierung als Mechanismus der Placeboresponse lassen sich keine unmittelbaren Implikationen für die klinische Praxis ableiten. Sollte es in zukünftigen Studien gelingen, die Konditionierbarkeit von Veränderung der Schlafarchitektur nachzuweisen, könnte eine Placebo kontrollierte Dosisreduktion (PCDR; Doering & Rief, 2012) eine mögliche Lösung für die Langzeitbehandlung der Insomnie darstellen.

5.5 Fazit

Insgesamt konnte die vorliegende Arbeit Belege für die differentielle Wirksamkeit verschiedener pharmakologischer Substanzklassen auf objektiven und subjektiven Zielvariablen liefern. Außerdem wurde ein substantieller Anteil von Placeboeffekten in der pharmakologischen Behandlung von primärer Insomnie nachgewiesen. Weiterhin gibt die Arbeit erste Anhaltspunkte für die dem Placeboeffekt in der Modulation der Schlafarchitektur zugrunde liegenden Mechanismen. Ob Veränderungen in der Schlafarchitektur tatsächlich konditionierbar sind, muss jedoch in weiteren Studien noch gezeigt werden. Insbesondere unter dem Aspekt des großen Anteils von Placeboeffekten an der Symptomverbesserung, könnte perspektivisch die systematische Nutzung und Optimierung von Placeboeffekten einen bedeutenden Fortschritt in der klinischen Praxis der pharmakologischen Insomnie-Behandlung darstellen.

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Appendix

Appendix A: Artikel 1

CNS Drugs (2014) 28:799–816
DOI 10.1007/s40263-014-0198-7

SYSTEMATIC REVIEW

Drug Treatment of Primary Insomnia: A Meta-Analysis of Polysomnographic Randomized Controlled Trials

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Published online: 29 August 2014

Abstract
Context Although insomnia is a frequent health complaint that is often treated with drugs, little is known about differences in treatment efficacy of various drug classes on objective versus subjective outcome measures.
Objective Our aim was to compare treatment efficacy of classical benzodiazepines, benzodiazepine receptor agonists (zopiclone, zolpidem and zaleplon), antidepressants (including low-dose doxepin), neuropeptides, progesterone receptor antagonists, hormones, melatonin receptor agonists, antihistamines, antiepileptics, and narcotics addressing primary insomnia.
Data Sources We conducted a comprehensive literature search (up to 5 April 2013) using PubMed, Cochrane Clinical Trials, PQDT OPEN, OpenGREY, ISI Web of Knowledge, PsycINFO, PSYNDEX, and the WHO International Clinical Trials Registry Platform.
Eligibility Criteria Only polysomnographic, parallel-group, randomized controlled drug trials were included; eligibility was determined by two independent authors.
Data Synthesis We used a random effects model, based on 31 studies reporting 80 treatment conditions, covering 3,820 participants.
Results Effect size estimates for the total sample of pooled drug classes suggest that there is a small-to-moderate, significant, and robust effect for objective outcomes (sleep onset latency $g = -0.36$, total sleep time $g = 0.27$) and subjective outcomes (sleep onset latency $g = -0.24$, total sleep time $g = 0.21$). Results indicate higher effect sizes for benzodiazepine receptor agonists and classical benzodiazepines compared with antidepressants (including low-dose doxepin) and for classical benzodiazepines compared with benzodiazepine receptor agonists. Benzodiazepine receptor agonists demonstrated higher effect sizes for objective outcomes.
Limitations Data on drug safety were not analyzed.
Conclusions Future studies should use objective and subjective assessment. Focusing on efficacy, clinicians should favor benzodiazepine receptor agonists and classical benzodiazepines over antidepressants (including low-dose doxepin) for primary insomnia treatment, but the additional consideration of different side effect profiles can lead to alternative treatment decisions.

Key Points

Benzodiazepine receptor agonists and classical benzodiazepines are significantly more effective than antidepressants (including low-dose doxepin) in reducing the sleep onset latency of patients suffering from primary insomnia.

Clinicians should take the diverse efficacy of different drug classes and their side effects profile into account.

Future studies should report objective and subjective assessments since sleep onset latency and total sleep time showed higher effect sizes for objective outcomes in the benzodiazepine receptor agonist subgroup.

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1 Introduction

Insomnia is a frequent health complaint [1] characterized by difficulties in initiating or maintaining sleep. In a representative sample, Leger et al. [2] found a prevalence of sleeping problems (during the past 12 months) of 56 % in the USA, 31 % in Western Europe, and 23 % in Japan. Depending on the diagnostic system under which insomnia is defined, estimates of its prevalence vary widely: in the American Insomnia Survey, prevalence rates range from 3.9 % under the *International Classification of Diseases*, 10th revision (ICD-10) to 22.1 % under the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (DSM-IV-TR) [3].

Almost half of the individuals suffering from sleep problems never see a physician to address these complaints. The majority of individuals with sleep problems who consult a physician receive pharmacotherapy [2]. Classical benzodiazepines and benzodiazepine receptor agonists (BZRAs; zopiclone, zolpidem, and zaleplon) are used in managing insomnia, but antidepressants are also used in clinical practice, although there is less evidence of their efficacy [4]. Therefore, evaluating the efficacy of different drug classes is highly relevant, and we address it in this paper.

Insomnia disorders have been categorized either as primary insomnia, where the sleep problem is the main disorder occurring independently of another mental disorder, or as comorbid insomnia, where the sleep problem is caused by another mental disorder, medical condition, or substance abuse [5]. Since treatment of comorbid insomnia is usually directed at the primary disorder and tackles the sleeping problem per se only in case of non-response or severe insomnia [5], we decided to focus on primary insomnia. However, under DSM-5 [6] the dichotomy of primary/comorbid insomnia has been replaced by the umbrella concept of 'insomnia disorder'.

Under DSM-IV-TR [7], primary insomnia is defined by the following criteria: (1) the predominant complaint is difficulty in initiating or maintaining sleep, or non-restorative sleep, for at least 1 month; (2) the sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning; (3) the sleep disturbance does not occur exclusively during the course of narcolepsy, breathing-related sleep disorder, circadian rhythm sleep disorder, or parasomnia; (4) the disturbance does not occur exclusively during the course of another mental disorder; (5) the disturbance is not due to the direct physiological effects of a substance. Since most primary studies used diagnostic criteria based on DSM-IV-TR, we refer to DSM-IV-TR instead of DSM-5 [6] criteria.

Current overviews addressing drug treatment efficacy in insomnia either did not analyze objective (polysomnographic) data, or they did include comorbid insomnia or did not include benzodiazepines, BZRAs, antidepressants, and other available drug classes in a comprehensive, single analysis [4, 8–16]. The comparison between different drug classes and between objective and subjective outcomes only has been addressed in some of these heterogenic overviews and on the whole they do not allow precise conclusions to be drawn. Thus, there is still insufficient evidence supporting the use of one drug class over another [17].

We therefore conducted a meta-analysis of randomized controlled drug trials that included polysomnographic assessments and were designed to examine the efficacy of all available drug treatments for primary insomnia, compare the efficacy of different drug classes, and compare their efficacy by objective versus subjective outcome measures. Additionally, we conducted moderator analyses to identify potential treatment moderators.

2 Method

For this meta-analysis, we referenced Meta-Analysis Reporting Standards (MARS) guidelines [18], including QUOROM (Quality of Reporting of Meta-Analyses) [19], PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [20], MOOSE (Meta-Analyses and Systematic Reviews of Observational Studies) [21] guidelines and the Potsdam Consultation on Meta-Analysis [22]. We did not use a review protocol. In "Appendix", we provide detailed information on quantitative data synthesis and moderator analyses.

2.1 Search Procedure

We identified studies by searching PubMed, Cochrane Clinical Trials, PQDT OPEN, OpenGREY, ISI Web of Knowledge, PsycINFO, PSYNDEX, and the WHO International Clinical Trials Registry Platform (ICTR). We conducted extensive searches for any studies published up to 5 April 2013 using the terms 'insomnia*' and 'placebo*' combined with the term 'polysomno*' as capable of identifying all polysomnographic, placebo-controlled drug trials independent of the drug class evaluated. In addition, we reviewed relevant journals and reference lists of relevant articles extracted from the database searches. We adopted comprehensive search strategies in order to find both published and unpublished articles. Additionally, we asked contacts involved with ICTR-registered clinical trials that fulfilled our inclusion criteria for data from their unpublished trials.

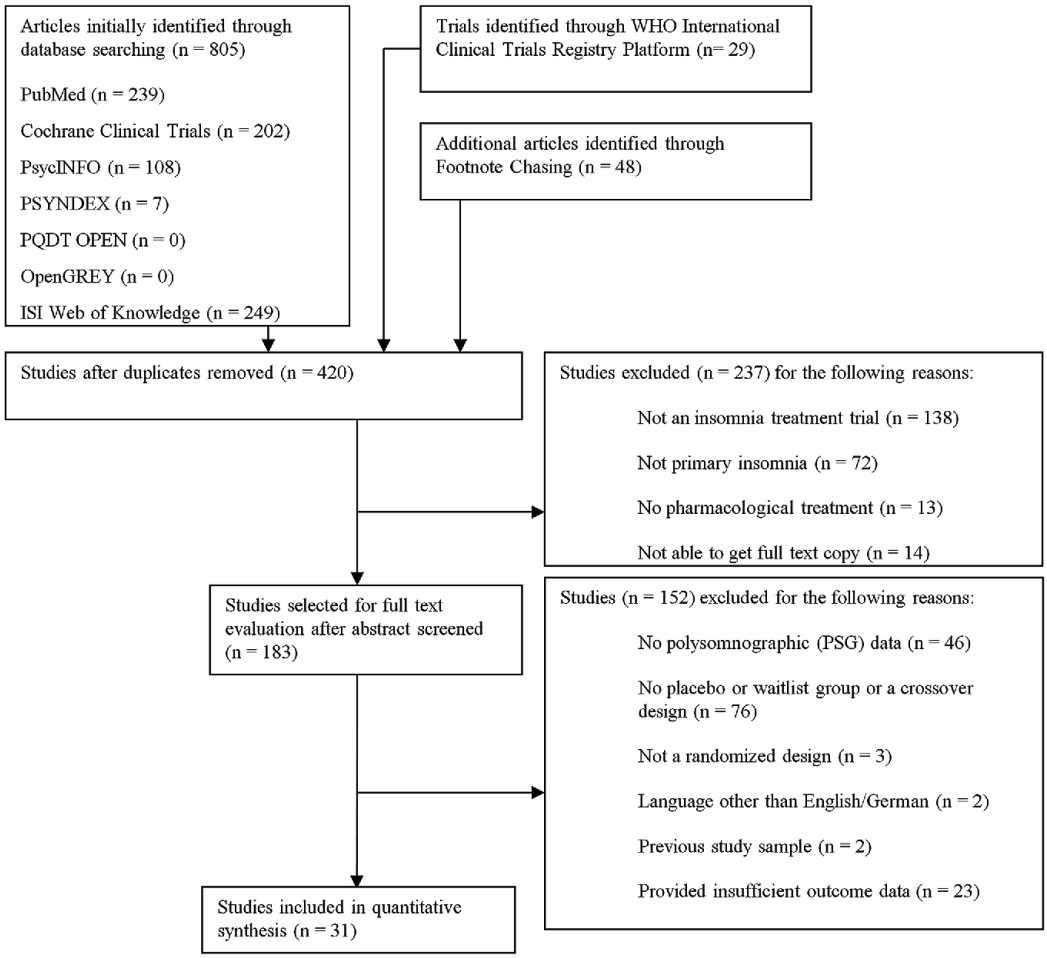

Fig. 1 Flow diagram of the study selection process

2.2 Determination of Outcome Variables

In a review, Morin [23] reported that there are still no standard assessment methods and criteria to define a successful outcome in the treatment of insomnia. While polysomnography is the gold standard for assessing sleep in clinical trials, it does not gather all the different facets of clinical insomnia. Therefore, it is essential to assess additional sleep diary data for a more subjective and experiential point of view to document treatment efficacy with multiple assessment modalities and multiple outcomes [23].

We chose 'total sleep time' (TST) and 'subjective TST' (sTST) as primary outcome variables, since a meta-analysis on polysomnography measures in insomnia [24] revealed that TST had strong differentiating power between patients with primary insomnia and good sleeper controls. The TST variable indicates objective (polysomnographic) assessment of data, while sTST comprises subjective data culled from sleep diaries and sleep questionnaires. As shown in Table 1, we chose 'sleep onset latency' (SOL), 'wake after sleep onset' (WASO) and "Sleep efficiency" (SE) as secondary objective outcome variables and 'subjective sleep onset latency' (sSOL), 'subjective WASO' (sWASO), 'subjective SE' (sSE) and 'sleep quality' (SQ) as secondary subjective outcome variables.

Table 1 Characteristics of included studies

References	*N* total (t*N*/c*N*)[a]	Drug in tx group (dose)	Class of drugs in tx group	Duration (days)	Average age in tx group	Females in tx group (%)	Outcome variables	Jadad quality score
Bes et al. [49]	16 *(8/8)*	DSIP (25 nmol/kg)	Neuropeptide	3	49.7	75	SQ, SE, SOL, WASO	2
Buckley et al. [50]	10 *(5/5)*	Mifepristone (600 mg)	Progesterone receptor antagonist	5	52.2	40	TST, WASO, SE	2
Fleming et al. [51]	141 *(106/35)*	Flurazepam (30 mg); zolpidem (10, 20 mg)	BDZ; BZRA	3	35 35 (35)	48 48 (48)	SE, SQ	3
Hajak et al. [52]	40 *(20/20)*	Doxepin (25–50 mg)	ADP	28	47.6	85	TST, SE, SOL	4
Herrmann et al. [53]	21 *(11/10)*	Zolpidem (10 mg)	BZRA	14	45	43	TST, SOL, WASO, SE, sTST, sSOL	3
Krystal et al. [54]	240 *(159/81)*	Doxepin (1, 3 mg)	ADP	85	71.3 (71.4)	65 (70)	TST, WASO, SE, SOL, sTST, sSOL, SQ	4
Krystal et al. [55]	229 *(153/76)*	Doxepin (3, 6 mg)	ADP	35	45.5 (44.2)	77 (71)	TST, WASO, SE, SOL	5
Luthringer et al. [56]	40 *(20/20)*	Prolonged-release melatonin (2 mg)	Hormone	21	59.6	35	TST, SOL, WASO, SQ	4
Mayer et al. [38]	335 *(159/176)*	Ramelteon (8 mg)	Melatonin receptor agonist	168	46.2	63.2	TST, sTST, sWASO, SQ	3
McCall et al. [57]	264 *(136/128)*	Eszopiclone (2 mg)	BZRA	14	71.5	64	TST, SOL, WASO, SE, sTST, sSOL, sWASO	4
Monti et al. [58]	12 *(6/6)*	Zolpidem (10 mg)	BZRA	15	53.8	100	TST, SOL, WASO, SE, sTST, sSOL	5
Monti et al. [59]	24 *(16/8)*	Zolpidem (10 mg); triazolam (0.5 mg)	BZRA; BDZ	27	44.6; 48.6	87.5; 87.5	TST, WASO	4
Monti et al. [60]	12 *(6/6)*	Zolpidem (10 mg)	BZRA	27	41.2	83	TST, SOL, WASO, SE, sTST, sSOL	3
Morin et al. [46]	35 *(17/18)*	Temazepam (7.5–30 mg)	BDZ	56	64.1	53	TST, WASO, SE, sTST, sWASO, sSE	5
Morin et al. [61]	184 *(119/65)*	Diphenhydramine (25 mg); valerian-hops (187 mg valerian + 41.9 mg hops)	Antihistamine	28	43.8; 43.9	60; 59.3	TST, SOL, SE, sTST, sSOL, sSE	3
Randall et al. [39]	91 *(44/47)*	Zolpidem (10 mg)	BZRA	224	50.18	52	TST, SE, SOL, WASO	4
Riemann et al. [62]	55 *(37/18)*	Trimipramine (50–200 mg); lormetazepam (1 mg)	ADP; BDZ	28	47; 45.3	47; 50	TST, SE, SOL, SQ	4
Roth et al. [63]	212 *(102/110)*	Zolpidem modified release (12.5 mg)	BZRA	21	43.6	62.7	WASO, SE, SOL	3
Roth et al. [64]	207 *(169/38)*	Tiagabine (2, 4, 6, 8 mg)	AED	2	70.9 (70.6; 71.3; 72.4)	42 (45; 51; 70)	TST, WASO, SOL, SE, sTST, sSOL, sWASO, SQ	3
Roth et al. [65]	30 *(20/10)*	Quazepam (7.5, 15 mg)	BDZ	7	68.8 (63.5)	30 (60)	TST, WASO, SOL	2
Scharf et al. [66]	75 *(51/24)*	Zolpidem (10, 15 mg)	BZRA	35	38 (38)	64 (64)	SOL, SE, sTST, sSOL, SQ	3
Schulz et al. [67]	14 *(8/6)*	Valerian (405 mg)		7	62	100	TST, SE, SOL	2

Table 1 continued

References	*N* total (t*N*/c*N*)[a]	Drug in tx group (dose)	Class of drugs in tx group	Duration (days)	Average age in tx group	Females in tx group (%)	Outcome variables	Jadad quality score
Sivertsen et al. [44]	28 *(16/12)*	Zopiclone (7.5 mg)	BZRA	42	61.3	37.5	TST, SE, sTST, sSE	5
Walsh et al. [68]	232 *(185/47)*	Tiagabine (4, 6, 8, 10 mg)	AED	2	44.9 (44.6; 40.7; 47.2)	70 (80; 56; 63)	TST, WASO, SOL, SE, sTST, sSOL, sWASO, SQ	3
Walsh et al. [69]	205 *(99/106)*	Zolpidem extended release (6.25 mg)	BZRA	21	70.3	61	WASO, SE, SOL	4
Walsh et al. [70]	113 *(56/57)*	Zaleplon (10 mg)	BZRA	35	41.8	71	TST, SOL, sTST, sSOL	5
Ware et al. [71]	110 *(73/37)*	Zolpidem (10 mg); triazolam (0.5 mg)	BZRA; BDZ	28	38; 38	58; 58	SOL, SE, WASO	4
Wu et al. [47]	34 *(17/17)*	Temazepam (7.5–30 mg)	BDZ	56	38	53	TST, SOL, SE, sTST sSOL, sSE	3
Xu et al. [37]	103 *(64/39)*	Propofol (3.0 g/l)	Narcotics	5	47.4	62.5	TST, SOL, WASO, SQ, sWASO	
Zammit et al. [72]	405 *(274/131)*	Ramelteon (8, 16 mg)	Melatonin receptor agonist	35	38 (40.2)	59 (66)	TST, SOL, SE, WASO, sTST, sSOL, SQ	3
Zammit et al. [73]	308 *(209/99)*	Eszopiclone (2, 3 mg)	BZRA	44	40.6 (38)	63.5 (73.3)	SOL, SE, WASO	4

Jadad quality score = quality scale (range 0–5 points, with a low value indicating poor study quality)

AED antiepileptic drug, *ADP* antidepressants, *BDZ* benzodiazepines, *BZRA* benzodiazepine receptor agonists, *DSIP* delta sleep-inducing peptide, *SE* sleep efficiency, *SOL* sleep onset latency, *SQ* subjective sleep quality, *sSE* subjective sleep efficiency, *sSOL* subjective sleep onset latency, *sTST* subjective total sleep time, *sWASO* subjective wake after sleep onset, *TST* total sleep time, *tx* treatment, *WASO* wake after sleep onset

[a] Number of subjects in the treatment condition and number of subjects in the control condition

2.3 Study Selection

A study was included if our screening of title and abstract showed it was an insomnia treatment trial, included a primary insomnia sample, and investigated pharmacotherapy. We excluded a study if text review showed that it lacked polysomnographic data, did not have the full text available, used a crossover design, or did not rely on a randomized design. Further grounds for excluding a study were lack of sufficient data for performing an effect size analysis, with no additional data available from the author; the full text was in a language other than English or German; or the sample overlapped, either partially or wholly, with the sample of another study included in the meta-analysis.

2.4 Data Extraction and Validity Assessment

For each study, two authors (CA and AW) extracted the data (Table 2) and study characteristics (Table 1). Only studies using a randomized controlled parallel-group design were included. Study quality was rated and considered as a moderator to control for possible confounders [25]. The Jadad quality scale was used for the validity assessment [26]. The two reviewers (CA and AW) separately assessed the quality of each study, and inter-rater reliability was calculated. Differences in assessments were resolved through discussion.

2.5 Quantitative Data Synthesis

All analyses were completed by using the Comprehensive Meta-analysis, version 2 software program [27]. We analyzed completer data in all cases. Separate effect sizes for the continuous variables SOL, TST, WASO, SE, sSOL, sTST, sWASO, sSE, and SQ were calculated using intervention group (IG)–comparison group (CG) differences for all studies. We calculated effect sizes using Hedges' *g* and its 95 % confidence interval (CI). Hedges' *g* is a variation of Cohen's *d* that corrects for bias due to small sample sizes [28]. Hedges' *g* can be interpreted using Cohen's recommendation for small (>0.20), medium (>0.50), and large effects (>0.80) [29].

To identify and quantify heterogeneity in effect sizes, we used a significance test based on the *Q* statistic and the ratio of true heterogeneity to total observed variation I^2 [30]. These methods are described in more detail in Borenstein

Table 2 Efficacy of pharmacological treatment for all outcomes

References	Treatment condition	Outcome variables	Between group comparisons			
			g	Standard error	95 % CI	*p* value
Bes et al. [49]	DSIP 25 nmol/kg	SE	0.38	0.48	−0.56, 1.31	0.431
		SOL	−0.59	0.48	−1.54, 0.35	0.220
		SQ	0.10	0.47	−0.83, 1.03	0.835
		WASO	−0.08	0.47	−1.01, 0.84	0.858
Buckley et al. [50]	Mifepristone 600 mg	TST	0.07	0.57	−1.05, 1.19	0.898
		SE	0.45	0.58	−0.69, 1.59	0.438
		WASO	−0.86	0.60	−2.04, 0.33	0.156
Fleming et al. [51]	Flurazepam 30 mg	SE	0.70**	0.24	0.23, 1.17	0.004
		SQ	0.85**	0.25	0.37, 1.33	0.001
	Zolpidem 10 mg	SE	0.31	0.24	−0.15, 0.78	0.191
		SQ	0.32	0.24	−0.15, 0.78	0.181
	Zolpidem 20 mg	SE	0.38	0.24	−0.09, 0.85	0.112
		SQ	0.25	0.24	−0.21, 0.72	0.289
Hajak et al. [52]	Doxepin 25–50 mg	TST	0.68*	0.32	0.05, 1.30	0.034
		SOL	−0.01	0.31	−0.62, 0.60	0.973
		SE	0.81*	0.32	0.18, 1.44	0.012
Herrmann et al. [53]	Zolpidem 10 mg	TST	0.54	0.43	−0.30, 1.38	0.204
		SOL	−0.85	0.44	−1.71, 0.01	0.054
		SE	0.77	0.44	−0.09, 1.62	0.079
		WASO	−0.22	0.42	−1.04, 0,61	0.607
		sTST	0.41	0.42	−0.42, 1.24	0.331
		sSOL	−0.77	0.44	−1.62, 0.09	0.079
Krystal et al. [54]	Doxepin 1 mg	TST	0.28	0.16	−0.03, 0.59	0.076
		SOL	−0.08	0.16	−0.39, 0.23	0.630
		SE	0.19	0.16	−0.12, 0.50	0.230
		WASO	−0.27	0.16	−0.58, 0.04	0.093
		sTST	0.40*	0.16	0.09, 0.71	0.012
		sSOL	−0.69**	0.16	−1.01, −0.37	<0.001
		SQ	0.52**	0.16	0.21, 0.84	0.001
	Doxepin 3 mg	TST	0.47**	0.16	0.16, 0.78	0.003
		SOL	−0.29	0.16	−0.60, 0.01	0.061
		SE	0.49**	0.16	0.18, 0.80	0.002
		WASO	−0.71**	0.16	−1.03, −0.40	<0.001
		sTST	0.48**	0.16	0.17, 0.79	0.002
		sSOL	−0.21	0.16	−0.51, 0.10	0.186
		SQ	0.52**	0.16	[0.21, 0.83]	0.001
Krystal et al. [55]	Doxepin 3 mg	TST	0.32*	0.16	0.00, 0.64	0.049
		SOL	−0.05	0.16	−0.36, 0.27	0.765
		SE	0.23	0.16	−0.08, 0.55	0.151
		WASO	−0.37*	0.16	−0.69, −0.05	0.022
	Doxepin 6 mg	TST	0.60**	0.16	0.27, 0.92	<0.001
		SOL	−0.29	0.16	−0.61, 0.02	0.070
		SE	0.36*	0.16	0.04, 0.68	0.026
		WASO	−0.50**	0.16	−0.82, −0.18	0.002
Luthringer et al. [56]	Prolonged-release melatonin 2 mg	TST	0.06	0.31	−0.55, 0.67	0.847
		SOL	−0.48	0.31	−1.10, 0.13	0.125
		WASO	−0.28	0.31	−0.89, 0.33	0.371
		SQ	0.40	0.31	−0.22, 1.01	0.206

Table 2 continued

References	Treatment condition	Outcome variables	Between group comparisons			
			g	Standard error	95 % CI	*p* value
Mayer et al. [38]	Ramelteon 8 mg	TST	0.04	0.09	−0.15, 0.22	0.708
		sTST	0.07	0.09	−0.11, 0.26	0.441
		sWASO	−0.26**	0.09	−0.45, −0.08	0.005
		SQ	0.11	0.09	−0.07, 0.30	0.234
McCall et al. [57]	Eszopiclone 2 mg	TST	0.51**	0.12	0.27, 0.75	<0.001
		SOL	−0.40**	0.12	−0.65, −0.16	0.001
		SE	0.51**	0.12	0.26, 0.75	<0.001
		WASO	−0.26*	0.12	−0.50, −0.02	0.036
		sTST	0.22	0.12	−0.02, 0.46	0.075
		sSOL	−0.15	0.12	−0.39, −0.09	0.222
		sWASO	−0.11	0.12	−0.35, 0.13	0.363
Monti et al. [58]	Zolpidem 10 mg	TST	0.90	0.56	−0.20, 2.01	0.110
		SOL	−1.30*	0.60	−2.47, −0.14	0.029
		SE	0.80	0.56	−0.30, 1.89	0.153
		WASO	−0.59	0.55	−1.66, 0.48	0.283
		sTST	0.20	0.53	−0.85, 1.25	0.711
		sSOL	−0.17	0.53	−1.22, 0.88	0.748
Monti et al. [59]	Triazolam 0.5 mg	TST	0.28	0.48	−0.65, 1.21	0.554
		WASO	−0.23	0.47	−1.16, 0.70	0.633
	Zolpidem 10 mg	TST	0.74	0.49	−0.22, 1.71	0.130
		WASO	−0.78	0.49	−1.74, 0.19	0.114
Monti et al. [60]	Zolpidem 10 mg	TST	0.58	0.55	−0.49, 1.65	0.285
		SOL	−0.52	0.54	−1.59, 0.54	0.335
		SE	0.56	0.55	−0.51, 1.63	0.303
		WASO	−0.80	0.56	−1.89, 0.29	0.151
		sTST	0.32	0.54	−0.73, 1.37	0.551
		sSOL	−0.08	0.53	−1.13, 0.96	0.876
Morin et al. [46]	Temazepam 7.5–30 mg	TST	0.66	0.34	−0.00, 1.33	0.051
		SE	0.69*	0.34	−0.03, 1.36	0.042
		WASO	−0.48	0.34	−1.14, 0.17	0.150
		sTST	0.38	0.33	−0.27, 1.04	0.249
		sSE	0.62	0.34	−0.04, 1.29	0.066
		sWASO	−0.70*	0.34	−1.36, −0.03	0.041
Morin et al. [61]	Diphenhydramine 25 mg	TST	0.01	0.18	−0.34, 0.36	0.949
		SOL	−0.58**	0.18	−0.94, −0.23	0.001
		SE	0.09	0.18	−0.26, 0.44	0.600
		sTST	0.17	0.18	−0.18, 0.52	0.330
		sSE	0.22	0.18	−0.13, 0.57	0.208
		sSOL	−0.00	0.18	−0.35, 0.35	0.990
	Valerian-hops	TST	0.09	0.18	−0.26, 0.44	0.601
		SOL	−0.43*	0.18	−0.78, −0.07	0.018
		SE	0.04	0.18	−0.31, 0.39	0.837
		sTST	0.07	0.18	−0.28, 0.42	0.686
		sSE	0.05	0.18	−0.30, 0.40	0.771
		sSOL	−0.15	0.18	−0.50, 0.20	0.414
Randall et al. [39]	Zolpidem 10 mg	TST	0.86**	0.22	0.43, 1.28	<0.001
		SOL	−1.14**	0.22	−1.58, −0.70	<0.001
		SE	0.91**	0.22	0.49, 1.34	<0.001
		WASO	−0.69**	0.21	−1.11, −0.27	0.001

Table 2 continued

References	Treatment condition	Outcome variables	Between group comparisons			
			g	Standard error	95 % CI	*p* value
Riemann et al. [62]	Lormetazepam 1 mg	TST	0.12	0.33	−0.52, 0.76	0.710
		SOL	−0.27	0.33	−0.92, 0.37	0.403
		SE	0.50	0.33	−0.15, 1.15	0.133
		SQ	0.80*	0.34	0.13, 1.46	0.018
	Trimipramine 50–200 mg	TST	0.56	0.33	−0.08, 1.20	0.088
		SOL	−0.41	0.33	−1.05, 0.23	0.208
		SE	0.77*	0.33	0.11, 1.42	0.021
		SQ	1.02**	0.34	0.35, 1.69	0.003
Roth et al. [63]	Zolpidem MR 12.5 mg	SE	0.11	0.14	−0.16, 0.38	0.437
		SOL	−0.23	0.14	−0.50, −0.04	0.093
		WASO	−0.33*	0.14	−0.60, −0.06	0.018
Roth et al. [64]	Tiagabine 2 mg	TST	0.01	0.22	−0.42, 0.45	0.953
		SOL	−0.26	0.22	−0.70, 0.17	0.240
		SE	0.01	0.22	−0.42, 0.45	0.948
		WASO	−0.14	0.22	−0.57, 0.30	0.540
		sTST	0.18	0.22	−0.26, 0.62	0.417
		sSOL	−0.18	0.22	−0.61, 0.26	0.424
		sWASO	−0.12	0.22	−0.56, 0.31	0.574
		SQ	0.31	0.22	−0.13, 0.75	0.163
	Tiagabine 4 mg	TST	0.04	0.23	−0.41, 0.48	0.864
		SOL	−0.22	0.23	−0.66, 0.23	0.339
		SE	0.04	0.23	−0.40, 0.49	0.855
		WASO	−0.07	0.23	−0.52, 0.37	0.756
		sTST	0.37	0.23	−0.08, 0.82	0.110
		sSOL	−0.12	0.23	−0.57, 0.32	0.583
		sWASO	−0.18	0.23	−0.63, 0.26	0.421
		SQ	0.16	0.23	−0.29, 0.61	0.483
	Tiagabine 6 mg	TST	0.14	0.22	−0.28, 0.57	0.509
		SOL	−0.28	0.22	−0.71, 0.15	0.203
		SE	0.15	0.22	−0.28, 0.58	0.495
		WASO	−0.31	0.22	−0.74, 0.12	0.159
		sTST	0.16	0.22	−0.27, 0.59	0.464
		sSOL	−0.12	0.22	−0.55, 0.30	0.569
		sWASO	−0.14	0.22	−0.57, 0.29	0.531
		SQ	0.16	0.22	−0.27, 0.59	0.457
	Tiagabine 8 mg	TST	0.05	0.22	−0.39, 0.49	0.820
		SOL	−0.05	0.22	−0.49, 0.39	0.819
		SE	0.05	0.22	−0.39, 0.49	0.825
		WASO	−0.11	0.22	−0.54, 0.33	0.636
		sTST	0.53*	0.23	0.08, 0.97	0.021
		sSOL	−0.05	0.22	−0.48, 0.39	0.837
		sWASO	−0.29	0.22	−0.73, 0.15	0.195
		SQ	0.14	0.22	−0.30, 0.58	0.527
Roth et al. [65]	Quazepam 15 mg	TST	0.85	0.45	−0.03, 1.73	0.059
		SOL	−0.56	0.44	−1.42, 0.30	0.199
		WASO	−0.62	0.44	−1.48, 0.24	0.157
	Quazepam 7.5 mg	TST	0.13	0.43	−0.71, 0.97	0.760
		SOL	−1.11*	0.46	−2.02, −0.21	0.016
		WASO	−0.19	0.43	−1.04, 0.65	0.651

Table 2 continued

References	Treatment condition	Outcome variables	Between group comparisons			
			g	Standard error	95 % CI	*p* value
Scharf et al. [66]	Zolpidem 10 mg	SE	0.51	0.28	−0.04, 1.07	0.070
		SOL	−0.70*	0.29	−1.26, −0.13	0.015
		sTST	0.21	0.28	−0.33, 0.76	0.445
		sSOL	−0.28	0.28	−0.83, 0.27	0.322
		SQ	0.32	0.28	−0.23, 0.87	0.252
	Zolpidem 15 mg	SE	0.61*	0.29	0.05, 1.18	0.033
		SOL	−0.60*	0.29	−1.17, −0.04	0.037
		sTST	0.51	0.29	−0.05, 1.07	0.076
		sSOL	−0.51	0.29	−1.07, 0.05	0.075
		SQ	0.36	0.28	−0.20, 0.91	0.210
Schulz et al. [67]	Valerian 405 mg	TST	0.38	0.51	−0.62, 1.38	0.458
		SOL	−0.02	0.51	−1.01, 0.97	0.972
		SE	0.29	0.51	−0.71, 1.28	0.573
Sivertsen et al. [44]	Zopiclone 7.5 mg	TST	0.71	0.38	−0.04, 1.46	0.065
		SE	0.18	0.37	−0.55, 0.91	0.626
		sTST	0.20	0.37	−0.53, 0.93	0.584
		sSE	0.17	0.37	−0.56, 0.89	0.656
Walsh et al. [68]	Tiagabine 10 mg	TST	0.07	0.20	−0.33, 0.47	0.734
		SOL	−0.05	0.20	−0.45, 0.35	0.803
		SE	0.06	0.20	−0.34, 0.46	0.767
		WASO	−0.02	0.20	−0.42, 0.38	0.933
		sTST	0.37	0.21	−0.03, 0.78	0.069
		sSOL	−0.20	0.21	−0.60, 0.20	0.327
		sWASO	−0.29	0.21	−0.70, 0.11	0.154
		SQ	0.28	0.21	−0.12, 0.69	0.168
	Tiagabine 4 mg	TST	0.05	0.21	−0.35, 0.46	0.795
		SOL	−0.16	0.21	−0.57, 0.24	0.427
		SE	0.06	0.21	−0.35, 0.46	0.787
		WASO	−0.17	0.21	−0.58, 0.23	0.402
		sTST	0.05	0.21	−0.35, 0.45	0.804
		sSOL	−0.19	0.21	−0.60, 0.21	0.353
		sWASO	−0.15	0.21	−0.55, 0.26	0.474
	Tiagabine 6 mg	TST	0.04	0.21	−0.36, 0.45	0.839
		SOL	−0.32	0.21	−0.73, −0.09	0.124
		SE	0.04	0.21	−0.36, 0.45	0.838
		WASO	−0.15	0.21	−0.56, 0.25	0.463
		sTST	0.11	0.21	−0.29, 0.52	0.583
		sSOL	−0.14	0.21	−0.54, 0.27	0.505
		sWASO	−0.16	0.21	−0.57, 0.25	0.439
		SQ	0.14	0.21	−0.26, 0.55	0.494
	Tiagabine 8 mg	TST	0.14	0.21	−0.27, 0.54	0.508
		SOL	−0.17	0.21	−0.57, 0.24	0.424
		SE	0.14	0.21	−0.27, 0.54	0.506
		WASO	−0.10	0.21	−0.51, 0.30	0.620
		sTST	0.03	0.21	−0.38, 0.43	0.896
		sSOL	−0.18	0.21	−0.59, 0.23	0.382
		sWASO	−0.10	0.21	−0.51, 0.30	0.624
		SQ	0.13	0.21	−0.27, 0.54	0.523
Walsh et al. [69]	Zolpidem ER 6.25 mg	SE	0.19	0.14	−0.08, 0.47	0.171
		SOL	−0.29*	0.14	−0.57, −0.01	0.039
		WASO	−0.30*	0.14	−0.57, −0.02	0.037

Table 2 continued

References	Treatment condition	Outcome variables	Between group comparisons			
			g	Standard error	95 % CI	*p* value
Walsh et al. [70]	Zaleplon 10 mg	TST	0.12	0.19	−0.25, 0.49	0.518
		SOL	−0.35	0.19	−0.72, 0.02	0.060
		sTST	0.20	0.19	−0.16, 0.57	0.276
		sSOL	−0.21	0.19	−0.57, 0.16	0.271
Ware et al. [71]	Triazolam 0.5 mg	SE	0.16	0.23	−0.30, 0.61	0.493
		SOL	−0.38	0.23	−0.84, 0.08	0.104
		WASO	−0.40	0.23	−0.86, 0.06	0.088
	Zolpidem 10 mg	SE	0.25	0.23	−0.20, 0.70	0.275
		SOL	−0.18	0.23	−0.63, 0.27	0.429
		WASO	−0.04	0.23	−0.49, 0.41	0.857
Wu et al. [47]	Temazepam 7.5–30 mg	TST	1.81**	0.40	1.02, 2.59	<0.001
		SOL	−1.71**	0.39	−2.49, −0.94	<0.001
		SE	0.97**	0.36	0.28, 1.67	0.006
		sTST	1.30**	0.37	0.58, 2.03	<0.001
		sSE	1.34**	0.37	0.61, 2.07	<0.001
		sSOL	−1.29**	0.37	−2.02, −0.57	<0.001
Xu et al. [37]	Propofol 3.0 g/l	TST	1.58**	0.23	1.13, 2.03	<0.001
		SOL	−1.63**	0.23	−2.08, −1.18	<0.001
		WASO	−3.26**	0.30	−3.86, −2.67	<0.001
		sWASO	−1.50**	0.23	−1.94, −1.05	<0.001
		SQ	3.37**	0.31	2.76, 3.97	<0.001
Zammit et al. [72]	Ramelteon 16 mg	TST	0.05	0.12	−0.19, 0.29	0.668
		SOL	−0.47**	0.12	−0.71, −0.23	<0.001
		SE	0.06	0.12	−0.18, 0.30	0.622
		WASO	−0.31*	0.12	−0.55, −0.07	0.012
		sTST	0.15	0.12	−0.09, 0.39	0.207
		sSOL	−0.14	0.12	−0.38, 0.10	0.267
		SQ	0.29*	0.12	0.05, 0.53	0.020
	Ramelteon 8 mg	TST	0.01	0.12	−0.23, 0.25	0.945
		SOL	−0.29*	0.12	−0.53, −0.05	0.017
		SE	0.01	0.12	−0.23, 0.25	0.934
		WASO	−0.21	0.12	−0.45, 0.03	0.081
		sTST	0.07	0.12	−0.17, 0.31	0.548
		sSOL	−0.43**	0.12	−0.67, −0.19	<0.001
		SQ	0.00	0.12	−0.24, 0.24	1.000
Zammit et al. [73]	Eszopiclone 2 mg	SE	0.32*	0.14	0.04, 0.59	0.024
		SOL	−0.23	0.14	−0.50, 0.05	0.109
		WASO	−0.21	0.14	−0.49, 0.06	0.132
	Eszopiclone 3 mg	SE	0.54**	0.14	0.26, 0.82	<0.001
		SOL	−0.61**	0.14	−0.89, −0.33	<0.001
		WASO	−0.24	0.14	−0.51, 0.04	0.090

The table shows effect size estimates (Hedges' *g*), the standard error, the 95 % CIs, and the significance test of between-group changes in all outcomes from before to after a pharmacological treatment of insomnia patients

CI confidence interval, *DSIP* delta sleep-inducing peptide, *ER* extended release, *MR* modified release, *SE* sleep efficiency, *SOL* sleep onset latency, *SQ* subjective sleep quality, *sSE* subjective sleep efficiency, *sSOL* subjective sleep onset latency, *sTST* subjective total sleep time, *sWASO* subjective wake after sleep onset, *TST* total sleep time, *WASO* wake after sleep onset

* $p < 0.05$. ** $p < 0.01$

et al. [31]. Effect size estimates for each outcome were pooled across studies to obtain a summary statistic based on a random effects model. We report the observed effect size with its CI separately for the total sample of pooled drug classes and for the subgroups of benzodiazepines, BZRAs, and antidepressants (including low-dose doxepin).

2.6 Sensitivity Analysis

To minimize publication bias, we conducted a careful search of the literature built on strategies for finding published and unpublished studies. The results of our meta-analysis are considered to be unbiased and robust if the constructed funnel plot of effect sizes is symmetrical, the Trim and Fill method [32] results in statistically significant re-calculated effect sizes, and the fail-safe N [33] exceeds $5K + 10$ (with K representing the number of studies included). We constructed a box plot for the mean effect sizes of all outcome variables in order to identify and exclude outliers if the distance to the average value of all effect sizes was three times or more the interquartile range.

2.7 Moderator Analyses

To address the problem of possible confounders of effect sizes [25, 34], we tested the moderating effect of study quality. Year of publication was chosen since technical developments in polysomnographic assessment may moderate the assessed treatment effect and a year-of-publication effect was demonstrated in a meta-analysis of antidepressant trials addressing patients with depression [35, 36]. Duration of treatment let us examine whether longer treatment was associated with greater or lesser treatment benefits. Age and percentage of female participants were chosen to examine (1) whether men and women and (2) younger and older participants obtained similar benefits from the treatment. We used meta-regression analyses (95 % CIs) to analyze these moderator effects.

2.8 Sub-Analyses on Drug Class

To compare the efficacy of the most frequently evaluated drug classes, we performed four separate analyses: (1) any pharmacological treatment, (2) benzodiazepine treatment alone, (3) BZRA treatment alone, and (4) antidepressant treatment alone.

In accordance with the convention we decided to classify doxepin as a tricyclic antidepressant because of its chemical structure. Although low doses of doxepin bind with high affinity to the histamine H1 receptor where it functions as an antagonist, we decided to include low-dose doxepin in the antidepressant subgroup since the active agent is the same in different doses of doxepin. The exact mechanism by which doxepin exerts its sleep maintenance effect is still unknown. We also reanalyzed size of the effects reported in the 25–50 mg doxepin trials, and this was comparable with the effect sizes in the 1–6 mg doxepin trials.

We chose a random effects model to combine studies within each subgroup. Q test assessed heterogeneity of different subgroups across studies.

3 Results

3.1 Study Selection

The initial search of databases identified 420 unique articles (Fig. 1) that we then examined for relevance. Screening of titles and abstracts produced a selection of 183 articles for full text evaluation. Of the 31 studies that ultimately met our selection criteria, one study [37] reported extremely large effect sizes and was therefore excluded from further analyses as an outlier. We did not encounter any unpublished studies that met our selection criteria. Of the 29 trials we identified at the ICTR, 14 studies reported insufficient outcome data, five studies used a crossover design, three studies did not report polysomnographic data, one study did not use a randomized design, one study reported data from a previous study sample, and, for five other studies, we were not able to get a full text copy of the results.

3.2 Study Characteristics

Tables 1 and 2 show in detailed fashion the breakdown of 80 treatment conditions as culled from the studies. They include 17 BZRA conditions (851 participants), six antidepressants (including low-dose doxepin) conditions (351 participants), eight antiepileptic conditions (349 participants), seven benzodiazepine conditions (152 participants), one antihistamine condition (60 participants), one hormone condition (20 participants), three melatonin receptor agonist conditions (433 participants), one narcotic condition (64 participants), one neuropeptide condition (eight participants), one progesterone receptor antagonist condition (five participants), two valerian conditions (67 participants), and 31 placebo conditions (1,460 participants). All the studies were published between 1992 and 2012. The number of treatment days ranged from 2 to 224 (M 36.16, standard deviation [SD] 47.14). For most studies, the duration of treatment was less than 3 months, with the exception of two studies that reported treatments lasting 168 days [38] and 224 days [39]. The total number of patients across all studies was 3,820, with 2,360 patients in treatment groups and the remaining 1,460 in control groups. The samples consisted predominantly of female participants (63.16 %). Participant ages ranged from 35 to 72 years (M 50.49 years, SD 11.73). The Jadad quality scores ranged from 2 to 5 points (M 3.52, SD 0.93),

Table 3 Effect sizes for all outcome variables of pooled drug classes and subgroups of drug classes

Outcome	*k*	*g*	95 % CI	Standard error	*z*	*p*	I^2	Fail-safe *N*	Obj. vs. sub. *Q*	*p*
Pooled drug classes										
TST	36	0.27**	0.17, 0.38	0.05	5.24	<0.001	46.58	487	0.95	0.330
SOL	39	−0.36**	−0.44, −0.27	0.04	−8.53	<0.001	33.40	1165	3.16	0.076
WASO	33	−0.29**	−0.36, −0.23	0.03	−8.50	<0.001	0.00	528	1.90	0.168
SE	41	0.29**	0.21, 0.37	0.04	7.17	<0.001	30.04	826	0.36	0.549
sTST	25	0.21**	0.14, 0.28	0.04	5.65	<0.001	0.00	215	0.95	0.330
sSOL	22	−0.24**	−0.34, −0.15	0.05	−5.16	<0.001	18.34	174	3.16	0.076
sWASO	11	−0.21**	−0.31, −0.10	0.05	−3.91	<0.001	0.00	30	1.90	0.168
sSE	5	0.41*	0.02, 0.79	0.20	2.07	0.038	63.45	10	0.36	0.549
SQ	22	0.28**	0.19, 0.38	0.05	5.68	<0.001	24.91	246	–	–
BDZ										
TST	6	0.64*	0.12, 1.16	0.26	2.42	0.015	62.13	19	0.13	0.717
SOL	5	−0.76**	−1.28, −0.24	0.27	−2.87	0.004	63.53	24	1.38	0.240
WASO	5	−0.40**	−0.70, −0.10	0.15	−2.60	0.009	0.00	3	0.63	0.428
SE	5	0.55**	0.27, 0.83	0.14	3.88	<0.001	17.25	21	1.14	0.285
sTST	2	0.83	−0.07, 1.73	0.46	1.81	0.071	70.60	–	0.13	0.717
sSOL	1	−1.29**	−2.02, −0.57	0.37	−3.50	<0.001	0.00	–	1.38	0.240
sWASO	1	−0.70*	−1.36, −0.03	0.34	−2.04	0.041	0.00	–	0.63	0.428
sSE	2	0.97**	0.26, 1.67	0.36	2.69	0.007	50.97	–	1.14	0.285
SQ	2	0.83**	0.44, 1.22	0.20	4.19	<0.001	0.00	–	–	–
BZRA										
TST	8	0.52**	0.33, 0.71	0.10	5.30	<0.001	10.85	59	4.34*	0.037
SOL	13	−0.46**	−0.61, −0.31	0.08	−5.93	<0.001	46.05	225	3.87*	0.049
WASO	11	−0.30**	−0.40, −0.19	0.06	−5.34	<0.001	0.00	72	1.86	0.172
SE	15	0.40**	0.28, 0.51	0.06	6.69	<0.001	18.27	205	0.38	0.537
sTST	8	0.25**	0.08, 0.42	0.09	2.95	0.003	0.00	9	4.34*	0.037
sSOL	7	−0.23**	−0.40, −0.06	0.09	−2.66	0.008	0.00	7	3.87*	0.049
sWASO	1	−0.11	−0.35, 0.13	0.12	−0.91	0.363	0.00	–	1.86	0.172
sSE	1	0.17	−0.56, 0.89	0.37	0.45	0.656	0.00	–	0.38	0.537
SQ	4	0.31*	0.06, 0.56	0.13	2.39	0.017	0.00	2	–	–
ADP										
TST	6	0.44**	0.29, 0.59	0.08	5.75	<0.001	0.00	47	0.00	0.968
SOL	6	−0.18*	−0.33, −0.03	0.08	−2.41	0.016	0.00	3	1.10	0.295
WASO	4	−0.46**	−0.65, −0.27	0.10	−4.80	<0.001	29.62	31	–	–
SE	6	0.38**	0.21, 0.54	0.08	4.50	<0.001	14.58	37	–	–
sTST	2	0.44**	0.22, 0.66	0.11	3.93	<0.001	0.00	–	0.00	0.968
sSOL	2	−0.45	−0.92, 0.03	0.24	−1.85	0.065	78.15	–	1.10	0.295
SQ	3	0.57**	0.36, 0.78	0.11	5.32	<0.001	0.00	21	–	–

ADP antidepressants, *BDZ* benzodiazepines, *BZRA* benzodiazepine receptor agonists, *CI* confidence interval, *fail-safe N* indicates the number of studies with a treatment effect of 0 that would be needed to lead to a non-significant overall result, I^2 ratio (0–100 %) 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 treatment conditions in the analysis, *Q* measure of heterogeneity to compare objective and subjective outcomes, *SE* sleep efficiency, *SOL* sleep onset latency, *sSE* subjective sleep efficiency, *sSOL* subjective sleep onset latency, *SQ* subjective sleep quality, *sTST* subjective total sleep time, *sWASO* subjective wake after sleep onset, *TST* total sleep time, *WASO* wake after sleep onset

* $p < 0.05$; ** $p < 0.01$

indicating that some studies suffered from methodological flaws; Cohen's Kappa inter-rater reliability was $\kappa = 0.812$.

3.3 Quantitative Data Synthesis

3.3.1 Efficacy of Pharmacotherapy for Primary Insomnia

Table 3 shows that all inter-group effect sizes (Hedges' g) for objective and subjective outcomes were significant for the total sample of pooled drug classes. All effects were small to medium, with CIs suggesting small-to-medium effects favoring pharmacotherapy over placebo for all outcome variables.

3.3.2 Efficacy of Different Subgroups of Pharmacotherapy for Primary Insomnia

Table 3 reveals that the comparisons for benzodiazepine versus placebo were significant for all outcome variables (with the exception of sTST). Effect sizes were small (g −0.40 for WASO) to large (g −1.29 for sSOL, based on a single study) for different outcome variables. As shown in Table 3, for comparisons between BZRA and placebo, all effect sizes (with the exception of sWASO and sSE) were significant. All effects involving different outcome variables were small (g −0.23 for sSOL) to medium (g 0.52 for TST). With the exception of sSOL, all effect sizes for comparisons between antidepressants and placebo were significant (Table 3). Effect sizes ranged from small (g −0.18 for SOL) to medium (g 0.57 for SQ) for different outcome variables.

The limited number of studies precluded evaluating fail-safe N for the effect sizes of all outcome variables in the subgroup analyses of different drug classes. However, most fail-safe Ns in the subgroup analyses did not exceed $5K + 10$. Therefore, we consider these effects sizes to be non-robust.

3.3.3 Comparison of Different Drug Classes

Table 4 shows that the Q test for heterogeneity yielded significant results for the comparison between benzodiazepines and BZRAs with regard to sSOL, and, in the case of SOL, for the comparisons between BZRAs and antidepressants as well as between benzodiazepines and antidepressants. For outcome variable SOL, benzodiazepines and BZRAs are significantly more effective than antidepressants and, for sSOL, benzodiazepines are more effective than BZRAs.

With respect to SQ, a significant Q test indicated that benzodiazepines are more effective than BZRA. Unfortunately, this finding cannot be interpreted due to an insignificant Q test for the heterogeneity between conditions.

3.3.4 Comparison of Objective Outcomes with Subjective Outcomes

Table 3 demonstrates larger effect sizes for objective outcomes in the BZRA subgroup for SOL/sSOL and TST/sTST. Analysis of CIs for the remaining objective and subjective outcomes and the results of the Q tests for heterogeneity yielded non-significant results. This indicates that there is no significant differential efficacy in improving insomnia between objective and subjective outcome measures in all other drug subgroups.

3.4 Sensitivity Analysis

With respect to the between-groups effect sizes of the total sample of pooled drug classes, all fail-safe Ns, except those for sWASO and sSE, exceeded $5K + 10$ and, accordingly, we considered them to be robust for purposes of this analysis. Concerning the sub-analyses of different drug classes, only fail-safe Ns of SOL, TST, WASO, and SE for BZRAs, and TST and WASO for antidepressants, exceeded $5K + 10$. Therefore, we did not consider the majority of effect sizes with respect to subgroup analysis to be robust (see Table 3).

The results of the Trim and Fill method suggest that the effect size estimates for all outcome variables (with the exception of sSE) were unbiased with respect to the total sample of pooled drug classes. We did not employ the Trim and Fill method for the subgroup analyses.

3.5 Moderator Analysis

As can be seen in Table 5, the treatment efficacy of the total sample of pooled drug classes was moderated by study quality with respect to TST and the mean age of the study sample with respect to TST and sTST. Studies of higher quality and studies with an older sample of patients reported higher effect sizes. None of the other potential moderators (year of publication, duration of treatment, percentage of female participants) significantly influenced the treatment effect.

4 Discussion

A principal finding of this meta-analysis is that benzodiazepines and BZRAs are significantly more effective than antidepressants in reducing SOL in patients with primary insomnia. Moreover, benzodiazepines are significantly more effective than BZRA in reducing sSOL of these patients. A second main finding is that SOL and TST (which are primary endpoints in most treatment studies addressing primary insomnia) showed higher effect sizes

Table 4 Between-group comparisons across different drug classes

Outcome	Between conditions		Within conditions		BDZ vs. BZRA		BDZ vs. ADP		BZRA vs. ADP	
	df	*Q*	*df*	*Q*	*df*	*Q*	*df*	*Q*	*df*	*Q*
Objective assessment										
TST	2	0.85	17	24.20	1	0.18	1	0.54	1	0.46
SOL	2	9.39**	21	36.13*	1	1.18	1	4.43*	1	6.70**
WASO	2	2.38	17	12.39	1	0.40	1	0.12	1	2.23
SE	2	1.20	23	27.82	1	1.00	1	1.14	1	0.04
Subjective assessment										
sTST	2	3.07	9	4.67	1	1.54	1	0.68	1	1.86
sSOL	2	8.21*	7	7.60	1	7.82**	1	3.68	1	0.70
sWASO	1	2.60	0	0.00	1	2.60	–	–	–	–
sSE	1	2.40	1	2.04	1	2.40	–	–	–	–
SQ	2	5.44	6	2.00	1	4.92*	1	1.33	1	2.50

ADP antidepressants, *BDZ* benzodiazepines, *Between conditions* overall difference between three conditions, *BZRA* benzodiazepine receptor agonists, *df* degrees of freedom, *Q* measure of heterogeneity, *SE* sleep efficiency, *SOL* sleep onset latency, *SQ* subjective sleep quality, *sSE* subjective sleep efficiency, *sSOL* subjective sleep onset latency, *sTST* subjective total sleep time, *sWASO* subjective wake after sleep onset, *TST* total sleep time, *WASO* wake after sleep onset, *within-condition* overall effect size heterogeneity

* $p < 0.05$; ** $p < 0.01$

for objective outcomes in the BZRA subgroup. Additionally, we found that the pooled effect sizes for all outcome variables were small to medium (with CIs suggesting small-to-medium effects) but were significant and robust for the majority of outcomes. These results buttress previous research [8, 9] that demonstrated a modest efficacy for pharmacological interventions in reducing symptoms of insomnia.

A number of limitations should nevertheless be kept in mind. First, even though there is a definition of primary insomnia, in practice it is difficult to differentiate between a sleep problem that exists independently of a mental disorder and one that does not. This means that the meta-analysis could be affected by a classification problem originating in the primary literature available to us. Our findings may still overestimate the effects of pharmacological treatment on primary insomnia, since our extensive, systematic search for unpublished data did not yield any that met our inclusion criteria. Since most studies did not report objective and subjective data for all outcome variables, the results of the meta-analyses may be biased, due to limited reporting of significant outcome variables in the primary literature.

Second, while we assessed the efficacy of different drug classes on primary insomnia in testing for statistically significant effect sizes, it remains unclear whether a statistically significant finding equates with a clinically significant improvement for patients with primary insomnia.

Third, while our review focused on comparing the efficacy of drug treatment on primary insomnia, we did not analyze data on drug safety, thus hindering a full cost-benefit analysis. The clinical usefulness is determined not only by the efficacy of a drug on sleep but also by its side effect profile. Abuse, dependency, tolerance, and rebound effects are clearly mentioned in the literature, especially on benzodiazepines, but also on BZRAs [4, 9, 40]. Antidepressants have a different quality of serious side effects, but have gained a fair market share in off-label use because they are not addictive. Therefore, a final recommendation of one drug class over another should always take the drug safety into account. Previous reviews that addressed drug safety concluded that, due to the modest efficacy of these medications, safety concerns dictated limiting their administration to the lowest necessary dose for the shortest required duration [8]. However, given the differences in efficacy among drug classes, an individual risk–benefit analysis that takes into account differences between drug classes and the type of primary insomnia-related sleeping problems would seem to be called for.

Fourth, there clearly is variance in treatment duration. To address this, we performed a moderator analysis on that variable. Nevertheless, it would be more informative to include only studies with more homogeneous treatment duration (e.g. 3–4 weeks). However, limiting our analysis to studies with this particular treatment duration would have excluded the majority of studies, resulting in biased and unrepresentative estimates of the current state of evidence, due to a gap of these studies in the literature.

Fifth, comparing objective and subjective data raises the question what is clinically relevant: polysomnography data

Table 5 Moderator analysis for pharmacological treatment on total sleep time and subjective total sleep time

Moderator	*k*	*β*	Standard error	*p* value
TST				
Quality of study	36	0.190**	0.05	0.000
Year of publication	36	−0.002	0.01	0.844
Duration of treatment	36	0.000	0.00	0.614
Mean age of sample	36	0.006*	0.00	0.039
% Females in study sample	36	−0.001	0.00	0.744
sTST				
Quality of study	25	0.075	0.07	0.264
Year of publication	25	−0.006	0.01	0.573
Duration of treatment	25	−0.000	0.00	0.511
Mean age of sample	25	0.006*	0.00	0.042
% Females in study sample	25	0.000	0.00	0.979

β estimated slope in meta regression analyses, *k* number of treatment conditions in the analysis, *sTST* subjective total sleep time, *TST* total sleep time,

* $p < 0.05$; ** $p < 0.01$

or subjective data from diaries and questionnaires? Morin [23] stated that different assessment modalities capture different dimensions of insomnia. While polysomnography data reflect a physiological dimension, data from sleep diaries reflect on the subjective complaint and perception of sleep. Therefore, a change in subjective data has probably more clinical relevance than a change in the physiology of a patient. Nevertheless, no single assessment instrument can capture all dimensions of insomnia treatment outcome [23].

Sixth, while our work focuses on the comparison of different drug classes it does not cover some details of pharmacodynamics. However, the topic of drug-receptor interactions in particular is very important, because there are differences in receptor binding according to different doses of the same drug. Therefore, future studies should go into more detail with respect to pharmacodynamics.

Seventh, merging together drugs with different compounds to generate subgroups of different drug classes (benzodiazepines, BZRAs, antidepressants) does not account for the pharmacokinetics of the different compounds. For instance, differences in elimination half-life (around 2.5 h for zolpidem [41] vs. around 6.0 h for eszopiclone [42]) are accountable for differences in the effect on SOL and TST.

Last, the generalizability of our findings is limited to the sample of patients with primary insomnia, and it is also constrained by the numerous methodological decisions made in the course of a meta-analysis.

Notwithstanding these methodological limitations, in contrast to earlier reviews, we were able to identify a sufficient number of treatment studies assessing polysomnographic outcomes to allow gathering an adequate sample of 31 trials with 80 treatment conditions covering a total of 3,820 participants. Hence, we were better able to compare the differential efficacies of drug treatment as measured by both objective and subjective outcomes.

Another strength of our study is that we addressed the problem of publication bias prophylactically through a careful search of the literature and retrospectively through different sensitivity analyses. We also analyzed study quality as a moderator, identified outliers and excluded them from our analyses. Finally, we used a random effects model to integrate the effect sizes, providing an opportunity to generalize our findings for a broader context.

The results of this study suggest that patients with primary insomnia may benefit from drug treatment. Clinicians should bear in mind that the efficacy of different drugs varies, indicating greater effect sizes for benzodiazepines and BZRAs in comparison with antidepressants with respect to SOL and sSOL. Nevertheless, the decision for a drug should always be based on the side effects profile in relation to a given patient and the efficacy of the drug.

Due to potential side effects, tolerance, and dependence, clinicians should also consider cognitive behavioral treatment for insomnia (CBT-I) as a treatment option. In their systematic review, Mitchell et al. [43] reported that CBT-I was at least as effective for treating insomnia and more durable when compared with pharmacological treatments, including five studies directly comparing drugs with CBT-I [44–48].

By including data on drug safety, the results of future meta-analyses can be improved still more. Future treatment studies should assess drug classes other than benzodiazepines, BZRAs, and antidepressants, and they should report objective and subjective data (even in the absence of statistically significant outcomes).

5 Conclusion

Several previous meta-analyses of insomnia drug treatments have been undertaken, although most of them were restricted to a few classes of drugs and types of outcomes (often without polysomnographic assessment). Therefore, our results can be regarded as an expansion of these studies in that they supply broader information on the differential efficacy of primary insomnia drug treatment as measured by objective and subjective outcomes.

Acknowledgments and Funding The study was prepared in the context of the FOR 1328 research unit on placebo and nocebo mechanisms and was supported by a grant from the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG). A Winkler, C Auer, BK Doering, and W Rief have no conflicts of interest including any financial, personal, or other relationships with other people or organizations to declare that could inappropriately influence, or be perceived to influence, the present work. This study did not require ethics approval.

Appendix

Detailed Information on Quantitative Data Synthesis and Moderator Analyses

Since comparative effectiveness research (CER) trials result in a higher clinical efficacy of the drug compared with conventional placebo-controlled trials [74], we decided a priori to restrict the searches to placebo-controlled trials.

The intergroup effect sizes were computed using the following formula: $d = \frac{\bar{X}_1 - \bar{X}_2}{\sqrt{\frac{(n_1-1)S_1^2+(n_2-1)S_2^2}{n_1+n_2-2}}}$, where $\bar{X}_1$ and $\bar{X}_2$ are the sample means, S_1 and S_2 are the SDs, and n_1 and n_2 are the sample sizes in the intervention condition and the control condition, respectively.

For studies reporting mean change, SD difference, and N in each group, the intergroup effect size was calculated using the following formula: $d = \frac{\bar{X}_1 - \bar{X}_2}{\sqrt{\frac{(n_1-1)S_1^2+(n_2-1)S_2^2}{n_1+n_2-2}}}$, where $\bar{X}_1$ and $\bar{X}_2$ are the sample mean changes, n_1 and n_2 are the sample sizes in the intervention condition and the control condition, respectively, and S_1 and S_2 are the SDs determined by the following formula: $S_x = \frac{\text{SDchange}_x}{\sqrt{2(1-r)}}$, where SD change$_x$ is the given SD change and r is the pre-post correlation. To calculate controlled effect sizes, the correlation between pre- and post-treatment measures is called for; however, it could not be determined from the study reports. As recommended by Rosenthal [33], we used a conservative estimate of $r = 0.70$ instead.

Hedges' g can be computed by multiplying d by a correction factor $J = 1 - \frac{3}{4df-1}$, where df is the degrees of freedom to estimate the intra-group SD.

Q is determined by the following formula: $Q = \sum_{i-1}^{k} W_i Y_i^2 - \frac{\left(\sum_{i=1}^{k} W_i Y_i\right)}{\sum_{i=1}^{k} W_i}$, with W_i being the weight of the study, Y_i the effect size of the study, and k the number of studies included. To determine the expected value of Q, we used the degrees of freedom ($df = k - 1$, with k being the number of studies included). A significant Q test (p value less than alpha set at 0.05) indicates heterogeneity in effect sizes.

I^2 is determined by using the following formula: $I^2 = \left(\frac{Q-df}{Q}\right) \times 100\ \%$. I^2 is expressed as a ratio, with a range of 0–100 %, and describes what proportion of the observed variance reflects real differences in effect sizes. Higgins et al. [30] suggest that values of 25, 50, and 75 % can be considered as low, moderate, and high, respectively.

We computed the fail-safe N using the following formula: $X = \frac{K(KZ^2-2.706)}{2.706}$, where K is the number of studies in the meta-analysis and $\bar{Z}$ is the mean Z obtained from the K studies. The effect size can be characterized as robust if the number of studies (X) required to reduce the overall effect size to a non-significant level exceeds $5K + 10$ [33].

We used the Trim and Fill method, which examines whether negative or positive trials are over- or under-represented, depending on the sample size. This information can then be used to re-calculate the effect size estimates, if the funnel plot is asymmetric. The divergence of the original effect size and the re-calculated effect size shows the degree of robustness of the results.

Instead of conducting a power analysis, we report the observed effect size with its CI, which is more informative than the statement that power was low [31]. We also did not report Ms and SDs for measurement artifacts because construct-level relationships were not the focus of this analysis.

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Appendix B: Artikel 2

pii: sp-00487-14 http://dx.doi.org/10.5665/sleep.4742

PLACEBO EFFECTS ON PSG PARAMETERS IN PRIMARY INSOMNIA: A META-ANALYSIS

Effect of Placebo Conditions on Polysomnographic Parameters in Primary Insomnia: A Meta-Analysis

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Study Objectives: Little is known about the role of placebo response in the pharmacotherapy of primary insomnia, especially about the effect of placebo intake on objectively assessed outcome variables. Our aim was therefore to conduct an effect-size analysis of placebo conditions in randomized controlled drug trials addressing primary insomnia also including polysomnography.

Design: We conducted a comprehensive literature search using PubMed, PsycINFO, PSYNDEX, PQDT OPEN, OpenGREY, ISI Web of Knowledge, Cochrane Clinical Trials, and the World Health Organization International Clinical Trials Registry Platform. The meta-analysis used a random effects model and was based on 32 studies reporting 82 treatment conditions covering a total of 3,969 participants. Special emphasis was given to the comparison of objective and subjective outcomes and the proportion of the placebo response to the drug response.

Measurements and Results: Effect sizes estimates (Hedges g) suggest that there is a small to moderate yet significant and robust placebo response reducing the symptoms of insomnia in terms of sleep onset latency (−0.35), total sleep time (0.42), wake after sleep onset (−0.29), sleep efficiency (0.31), subjective sleep onset latency (−0.29), subjective total sleep time (0.43), subjective wake after sleep onset (−0.32), subjective sleep efficiency (0.25) and sleep quality (0.31). Thus, the placebo response was also evident in objective, physiological (polysomnographic) variables. Our results indicate that 63.56% of the drug responses are achieved even in the placebo groups.

Conclusions: In light of these strong placebo responses, future studies should investigate how to exploit placebo mechanisms in clinical practice.

Keywords: insomnia, meta-analysis, placebo, polysomnographic, review, treatment

Citation: Winkler A, Rief W. Effect of placebo conditions on polysomnographic parameters in primary insomnia: a meta-analysis. *SLEEP* 2015;38(6):925–931.

INTRODUCTION

Primary insomnia is a frequent health complaint defined by difficulty in initiating or maintaining sleep, or nonrestorative sleep, for at least 1 month causing clinically significant distress or impairment in social, occupational, or other important areas of functioning. Symptoms do not occur exclusively during the course of narcolepsy, breathing-related sleep disorder, circadian rhythm sleep disorder, parasomnia, another mental disorder, or due to a drug's direct physiological effects.[1]

In the American Insomnia Survey, prevalence rates range from 3.9% under International Classification of Diseases (ICD)-10 to 22.1% under Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR).[2] Because most primary studies applied diagnostic criteria based on DSM-IV-TR, we refer to DSM-IV-TR[1] instead of DSM-V[3] criteria.

Although almost half the individuals suffering from sleep problems never see a physician to address their complaints, most who consult a physician receive pharmacotherapy (approximately 50% in Western Europe or the United States, and up to 90% in Japan) to address their sleep problems.[4] Although there is solid evidence of the efficacy of sleeping pills,[5] the effect size only appears moderate, and it is unclear how large the placebo response is in relation to the drug response. Moreover, the benefit-risk ratio is frequently critical; for instance, the modest efficacy of hypnotics[6] is accompanied by the risk of serious side effects and dangers such as cognitive effects, daytime fatigue, tolerance, addiction, risk of falls, fractures, depression, suicide, and increased mortality.[7–9]

Other areas of research reveal evidence that the placebo response accounts for up to 75% of the treatment effect in antidepressant trials and up to 50% in pain or generalized anxiety disorder trials.[10] Although pain or depression research is mainly based on subjective outcome variables, the subject of insomnia enables us to compare subjective and objective outcome parameters in the placebo group. It is frequently postulated that placebo responses are mainly detected in subjective scores, whereas the placebo groups in insomnia trials allow the comparison of subjective placebo responses with objective polysomnographic outcome variables.

Concerning insomnia trials, there have been three meta-analyses finding evidence of significant improvements under placebo conditions.[7,11,12] Recent studies either did not report any effects in the placebo groups on objective outcome parameters (but they mainly focused on subjective aspects of sleep quality), or they suffer from small sample sizes and the lack of objective polysomnographic (PSG) data. Additionally, the proportion of the placebo response on drug response to different drug classes remains unclear.

We therefore conducted a meta-analysis of placebo conditions in PSG randomized controlled drug trials to examine the efficacy of placebo treatment for primary insomnia, to compare its efficacy on objective versus subjective outcome measures, and to determine its proportion in the response to pharmacological treatments. We conducted moderator analyses to identify potential treatment moderators.

Submitted for publication July, 2014
Submitted in final revised form October, 2014
Accepted for publication October, 2014
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METHODS

For this meta-analysis we adhered to Meta-Analysis Reporting Standards (MARS) guidelines.[17] In addition to the assessment of within group changes in the placebo conditions, the identified primary literature was furthermore used for an analysis of between group comparisons to determine the efficacy of drug treatment of primary insomnia.

Search Procedure

We identified studies by searching PubMed, PsycINFO, PSYNDEX, PQDT OPEN, OpenGREY, ISI Web of Knowledge, and the Cochrane Clinical Trials Library. We conducted extensive searches for studies published between the first available year and April 5, 2013 using the terms *insomnia** and *placebo** combined with the term *polysomno**.

In addition, we searched the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTR), a manual review of relevant journals, and did a manual review of reference lists of relevant articles and review papers extracted from the database searches. We adopted comprehensive search strategies in order to identify both published and unpublished articles (including asking the contact persons in all clinical trials at the ICTR for data from their unpublished trials).

Determination of Outcome Variables

We chose "Sleep Onset Latency" (SOL) and "subjective Sleep Onset Latency" (sSOL) as core outcome variables. We also included "Total Sleep Time" (TST), "Wake After Sleep Onset" (WASO), and "Sleep Efficiency" (SE) as additional objective outcome variables (assessed with PSG recordings) and "subjective TST" (sTST), "subjective Wake After Sleep Onset" (sWASO) and "Sleep Quality" (SQ) as additional subjective outcome variables (assessed with sleep diaries and sleep questionnaires). These are established outcome variables in insomnia treatment trials.

Study Selection

Only pharmacological treatment trials addressing primary insomnia were considered via title and abstract screening. Studies were excluded after full text screening if no PSG data or insufficient data to perform an effect-size analysis were reported or a waitlist control condition was used instead of a placebo control condition. Studies were also excluded if the sample overlapped, either partially or wholly, with the sample of another study already included in the meta-analysis. Moreover, the study had to have used a double-blind randomized parallel group design using a placebo control condition, and the entire text had to be available in the English or German language.

We made no restrictions on sample size, treatment duration, or publication date because of the anticipated small number of studies using PSG data. We also made no geographical or cultural restrictions because we were interested in a global perspective on insomnia and its treatments.

Because our focus was on changes in the placebo control conditions instead of changes in the drug condition of primary insomnia trials, we made no restrictions on drug classes and decided to include trials assessing drugs not established for insomnia therapy if the study reported data for a placebo control condition separately.

Each identified article was further examined by two independent, experienced researchers for potential inclusion in the meta-analysis. Disagreements were resolved by discussion.

Validity Assessment

Only studies using a randomized controlled parallel group design were included. Nevertheless, we rated the quality of each study and analyzed study quality as a moderator to control for possible confounds.[18] We therefore used the Jadad quality scale,[19] which consists of seven dichotomous items with a maximum score of five and assesses aspects of validity. Each study's quality was assessed independently by two trained researchers, and interrater reliability was calculated. Disagreements were resolved through discussion.

Data Extraction

For each study, data and the following study characteristics were extracted from each study collectively by two independent trained experts: total N, N of treatment group, N of control group, drug in treatment group, dose of treatment drug, class of drug in treatment group, duration of treatment, average age in placebo group, and percentage of female participants in placebo group. In case of missing data on age or percentage of female participants in subgroups, we used age and percentage of female participants in the total sample as an estimator. In cases of missing data on individual moderator variables, the relevant study was excluded only from the analysis of that moderator variable. Disagreements were resolved through discussion.

Quantitative Data Synthesis

All analyses were completed by using the software program "Comprehensive Meta-analysis, version 2."[20] We analyzed completer data in all cases. Separate within-group effect sizes for the continuous variables SOL, TST, WASO, SE, sSOL, sTST, sWASO, and SQ were calculated using within-group changes of placebo and drug conditions (for detailed information see supplemental material). We calculated effect sizes using Hedges *g* and its 95% confidence interval. Hedges *g* is a variation of Cohen *d* that corrects for bias due to small sample sizes.[17] The magnitude of Hedges *g* can be interpreted using Cohen's recommendation for small (0.20), medium (0.50), and large (0.80).[18] We followed Rosenthal's recommendation[16] and used a conservative estimate of $r = 0.70$ for the correlation between pretreatment and posttreatment measures.

We used a test of significance based on the *Q* statistic to identify heterogeneity in effect sizes. Furthermore, we estimated the variance of the true effect between the studies (T^2) to quantify heterogeneity in effect sizes. In addition, we used the ratio of true heterogeneity to total observed variation I^2.[20] These methods are described in more detail in Borenstein, Hedges[21].

Effect size estimates for SOL, TST, WASO, SE, sSOL, sTST, sWASO, and SQ were pooled across studies to obtain a summary statistic. The effect size estimates were calculated using a random effects model.[22] Instead of conducting a power analysis, we report the observed effect size with its confidence interval.[16] For the purposes of conducting subgroup analyses, we chose a random effects model and used the Q test for heterogeneity across studies to compare the effects of different subgroups.

We used a method described by Kirsch and Sapirstein[25] and subtracted the mean placebo response rates from mean drug response rates to determine the proportion of placebo response to drug response to pharmacological treatment.

Sensitivity Analysis

To minimize publication bias, we conducted a careful literature search that included strategies to find published and unpublished studies. The results of our meta-analysis were considered to be unbiased and robust if the funnel plot for the effect sizes was symmetrical, the trim and fill method[34] resulted in statistically significant recalculated effect sizes, and the fail-safe N[35] exceeded $5K+10$ (with K representing the number of studies included). We treated effect sizes as outliers if the distance to the average value of all effect sizes was 1.5 times the interquartile range or more.

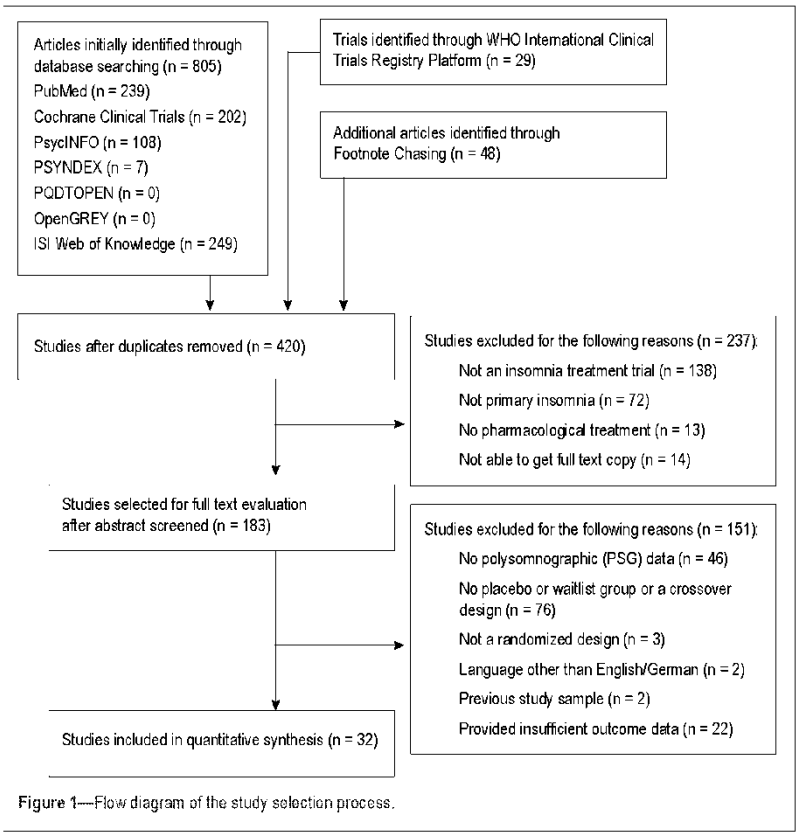

Figure 1—Flow diagram of the study selection process.

Moderator Analyses

The moderating effect of study quality was tested to address the problem of possible confounds of effect sizes[4,25] due to differences in methodological quality across studies, which is known in the literature as the garbage in/garbage out problem.[21] Year of publication was chosen as a potential moderator because we wanted to know whether the methodological and technical developments in primary PSG studies moderate the treatment effect. Duration of treatment was chosen as a potential moderator to examine whether participants who received treatment for a longer period of time gained more or less benefit from the placebo treatment. Average age and percentage of female participants were chosen as potential moderators to examine (1) whether men and women or (2) younger and older participants gained the same benefit from the placebo treatment. Moderator effects were examined using meta-regression analyses (95% confidence intervals).

RESULTS

Study Selection

As Figure 1 shows, our initial search of databases identified 420 unique articles examined for relevance. After screening titles and abstracts, we selected 183 articles for full text evaluation. None of the 32 included studies fulfilling our selection criteria[25–57] reported unusually high effect sizes with respect to the placebo group. The studies included in the meta-analysis included 82 treatment conditions and covered a total of 3,969 participants. None of the unpublished studies we found met our selection criteria. A table providing descriptive information on each included study can be requested from the corresponding author.

Study Characteristics

The 82 pharmacological treatment conditions include 17 hypnotic drugs (851 participants), 6 antidepressants (351 participants), 8 antiepileptics (349 participants), 7 benzodiazepine conditions (152 participants), 1 antihistamine condition (60 participants), 2 gamma-aminobutyric acid GABA receptor modulator conditions (105 participants), 1 hormone condition (20 participants), 3 melatonin receptor agonist conditions (433 participants), 1 narcotic condition (64 participants), 1 neuropeptide condition (8 participants), 1 progesterone receptor antagonist condition (5 participants), 2 valerian conditions (67 participants), and 32 placebo conditions (1,504 participants).

All studies were published between 1992 and 2012. The number of days of intervention ranges from 2 to 224 (mean [M] = 31.72, standard deviation [SD] = 42.35). The total number of patients across all studies was 3,969 with 2,465 patients in treatment and the remaining 1,504 in control groups. The

Table 1—Pooled Within-Group Effect Sizes for Placebo Treatment.

Outcome	k	g	95% CI	z	P	I^2	Fail-Safe N	Obj. vs. Sub. Q	Obj. vs. Sub. P
Objective outcomes									
SOL	26	−0.35**	−0.42, −0.28	−9.69	< 0.001	52.52	1,324	0.832	0.362
TST	25	0.42**	0.29, 0.55	6.38	< 0.001	83.18	1,765	0.019	0.891
WASO	22	−0.29**	−0.38, −0.19	−5.67	< 0.001	71.87	636	0.209	0.648
SE	25	0.31**	0.19, 0.43	5.11	< 0.001	82.91	1,079	0.397	0.529
Subjective outcomes									
sSOL	12	−0.29**	−0.39, −0.19	−5.62	< 0.001	53.39	213	0.832	0.362
sTST	15	0.43**	0.34, 0.52	8.97	< 0.001	57.55	771	0.019	0.891
sWASO	6	−0.32**	−0.41, −0.22	−6.61	< 0.001	33.01	95	0.209	0.648
sSE	4	0.25**	0.11, 0.40	3.50	< 0.001	0.00	10	0.397	0.529
sQuality	11	0.31**	0.16, 0.46	4.07	< 0.001	79.79	289	–	–

*P < 0.05. **P < 0.01. CI, confidence interval; k, number of treatment conditions in the analysis; 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); Fail-Safe N, indicates the number of studies with a treatment effect of 0 that would be needed to lead to a nonsignificant overall result; Obj., objective; Q, measure of heterogeneity to compare objective and subjective outcomes; SE, sleep efficiency; SOL, sleep onset latency; sQuality, subjective quality; sSE, subjective sleep efficiency; sSOL, subjective sleep onset latency; sTST, subjective total sleep time; sWASO, subjective wake after sleep onset; Sub., subjective; TST, total sleep time; WASO, wake after sleep onset.

samples were predominantly female (63.23%). The average age of participants ranges from 35 to 72 (M = 51.24, SD = 12.15 for all patients, M = 51.58, SD = 11.46 for patients in placebo groups). The Jadad quality scores ranged from 2 to 5 points (out of a maximum of 5 points; M = 3.73, SD = 0.54). We used two independent quality ratings, with Cohen kappa interrater reliability[53] of κ = 0.794.

Quantitative Data Synthesis

Table 1 shows that the pooled within-group effect sizes (Hedges *g*) of the placebo conditions for SOL (26 studies), TST (25 studies), WASO (22 studies), SE (25 studies), sSOL (12 studies), sTST (15 studies), sWASO (6 studies), sSE (4 studies), and sQuality (11 studies) were significant. According to Cohen's interpretation recommendations, all effects were small-to-medium with confidence intervals suggesting small-to-medium and medium-to-large effects for TST and sTST, respectively.

Sensitivity Analysis

Table 1 also illustrates that all fail-safe Ns (with the exception of sSE) exceeded 5K+10 and, accordingly, we considered these effect sizes to be robust regarding this analysis. Trim and Fill method results suggest that the effect size estimates for all considered outcome variables were unbiased.

Moderator Analysis

To take into account the variance of effect sizes from study to study (see Table 1) and to explore possible predictors of placebo treatment outcome, we conducted a moderator analysis for all pooled effect sizes. None of the chosen potential moderators (study quality, year of publication, duration of treatment, average age, and percentage of female participants) showed appreciable and significant moderation of the placebo treatment effect.

Comparison of Objective Outcomes with Subjective Outcomes

As Table 1 shows, the confidence intervals of objective and subjective outcomes overlapped in each comparison, and results from the *Q* tests for heterogeneity between subgroups yielded nonsignificant results from each comparison, which indicates no significant differences in the efficacy of improving insomnia between objective and subjective outcome measures.

Proportion of the Placebo Response to the Drug Response

Table 2 shows that subtracting the mean placebo response rates from mean drug response rates revealed that 39% (sSE) to 100% (sWASO) of the response to the medications under investigation are reported in the placebo group as well. In fact, one outcome variable (sWASO) placebo treatment was even more effective than the pharmacological therapy. The pooled proportion of the placebo response to the drug response was 63.56% (SD = 20.92).

DISCUSSION

Results indicated that the pooled effect sizes of placebo treatment for all outcome variables were small to medium, but significant and robust. Moreover, we detected no significant differences in the efficacy of placebo treatment between objective (PSG) and subjective (sleep diary and questionnaires) assessments. Thus placebo responses were also detectable in association with objective variables like the PSG parameters. With respect to the proportion of the placebo response to the drug response, our results reveal that 63.56% (SD = 20.92) of the response to the medications are achieved even in the placebo group.

The finding of a significant placebo response in pharmacological interventions for primary insomnia stands in line with Huedo-Medina, Kirsch[7] reporting that the placebo response is a major contributor to the efficacy of nonbenzodiazepine hypnotics, but it ought to be generalized to all pharmacological

treatments for insomnia. It also supports findings by McCall, D'Agostino[13] reporting a significant improvement in sSOL and sTST in the placebo groups of five drug trials and Belanger, Vallieres[12] reporting significant improvements in 23 placebo conditions compared to seven waitlist conditions from different trials with respect to subjective parameters (sSOL and sTST).

The conclusion whether placebo responses were also detectable in association with objective variables was equivocal in earlier studies, with Huedo-Medina, Kirsch[7] reporting significant effect sizes for both subjective and objective SOL, whereas McCall, D'Agostino[13] did not report significant changes with respect to objective (polysomnographic) data. Belanger, Vallieres[12] detected no significant group differences in their between-group comparison's objective data, although they did report a significant within-group improvement in subjective outcomes (sSOL, sWASO, sTST, sSQ) and in objective outcomes (SOL, SE). These heterogeneous findings may be attributable to the limited number of studies included that assessed objective data in previous reviews.

Table 2—Pooled Within-Group Effect Sizes for Drug Treatment and Proportion of Placebo Response to Drug Response.

Outcome	k	g	95% CI	P	Placebo response (%)
Objective outcomes					
SOL	41	−0.55**	−0.63, −0.46	< 0.001	64
TST	38	0.79**	0.69, 0.88	< 0.001	53
WASO	35	−0.55**	−0.66, −0.44	< 0.001	53
SE	41	0.64**	0.55, 0.73	< 0.001	48
Subjective outcomes					
sSOL	22	−0.45**	−0.57, −0.34	< 0.001	64
sTST	25	0.54**	0.42, 0.65	< 0.001	80
sWASO	11	−0.29**	−0.42, −0.16	< 0.001	100
sSE	5	0.64**	0.39, 0.89	< 0.001	39
sQuality	22	0.51**	0.37, 0.65	< 0.001	61

*P < 0.05. **P < 0.01. CI, confidence interval; k, number of treatment conditions in the analysis; Placebo Response, proportion of placebo effect to pre-post pharmacological effect in percent; SE, sleep efficiency; SOL, sleep onset latency; sSE, subjective sleep efficiency; sQuality, subjective quality; sSOL, subjective sleep onset latency; sTST, subjective total sleep time; sWASO, subjective wake after sleep onset; Sub., subjective; TST, total sleep time; WASO, wake after sleep onset.

Our results reinforce the evidence that placebo responses were also detectable in conjunction with objective variables—an important contribution to the current pool of evidence in placebo research, because most studies investigating placebo mechanisms have addressed placebo analgesia without having evaluated objective outcomes. Beyond the PSG parameters in insomnia research, there are few clinical examples (e.g., Parkinson disease and hypertension) enabling comparison of such a placebo response in objective and subjective data.[59–61]

Our results indicate that 63.56% of the response to the medications examined may have been a placebo response. That is a key finding, because a great proportion of the therapeutic effect could also be achieved by optimizing placebo mechanisms. Regression to the mean, expectancy, social desirability,[62] actual ingestion of the inert pill,[62] the Hawthorne effect, cognitive dissonance, participation in research, and physiologic changes produced by placebos[64] are discussed as contributors to the placebo response.[62–64] In their review on the placebo response in medicine, Enck, Bingel[65] reported several strategies to optimize placebo responses via the management of patients' expectations, the use of conditioning strategies (e.g., placebo-controlled dose reduction[65]), and improving the physician-patient relationship. Against the background of our results, those strategies may also improve outcomes in the treatment of primary insomnia.

Nevertheless, a number of limitations should be noted. Examining intragroup changes in our analysis may have led to a biased estimate of the effect size due to additional influences such as natural history and regression to the mean.[57] However, natural history seems less likely in the case of primary insomnia, because insomnia symptoms tend to become chronic.[66] Furthermore, there is a lack of studies including both a placebo and a waitlist condition in the same trial. Therefore, limiting our analysis to intergroup comparisons would have ruled out all the studies we included, making it impossible to determine the current state of evidence.

To compute the proportion of placebo response to the drug response, we subtracted the placebo condition's pooled effect size from that of the drug condition. This approach depends on assuming the additivity of natural course effects, placebo effects, and drug effects, a model that is being increasingly questioned.[67] Therefore, other options to analyze genuine placebo responses should also apply (e.g., "hidden application designs" and the further experimental manipulation of placebo mechanisms).

The methods we used to test the potential effect of publication bias are no equivalent alternative to including unpublished studies. Unfortunately, we were unable to find unpublished studies meeting our inclusion criteria even though we did an extensive and systematic search for unpublished data. However, in contrast to drug conditions, regarding placebo conditions in clinical trials it is highly unlikely whether a publication bias exists, as that would mean that studies with larger effect sizes in the placebo condition tend to be published more frequently.

We used the same assessment periods for objective (PSG) and subjective sleep parameters whenever the same time points were reported in the primary literature. In a minority of studies subjective estimates were derived from different and longer assessment periods (up to 2 w before the intervention to 2-w follow-up) than objective estimates limiting their comparability.

The strength of our study is a comprehensive search of the literature to preventively minimize publication bias. In comparison with previous reviews, we could identify several

additional treatment studies, especially additional studies assessing objective (PSG) outcomes. This enabled us to investigate whether placebo responses were also detectable in objective variables and to compare objective and subjective data based on an adequate sample of studies. Additionally, we were able to determine the proportion of the placebo response to the drug response to pharmaceuticals in different drug classes.

To conclude, further research on insomnia treatment should retain placebo control conditions and add waitlist conditions in the same clinical trial. Further studies on placebo mechanisms should utilize options independent from the assumption of additivity to analyze the proportion of placebo response to drug response. Most notably, attempts should be undertaken to exploit placebo mechanisms in clinical practice.

DISCLOSURE STATEMENT

This was not an industry supported study. The study was prepared in the context of the FOR1328 research unit on placebo and nocebo mechanisms and was supported by a grant from the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG). The authors have indicated no financial conflicts of interest. The study was prepared in the context of the FOR1328 research unit on placebo and nocebo mechanisms and was supported by a grant from the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG). A Winkler and W Rief have no conflicts of interest including any financial, personal or other relationships with other people or organizations to declare that could inappropriately influence, or be perceived to influence, the present work. This study did not require ethics approval.

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SUPPLEMENTAL MATERIAL

Detailed Information on Quantitative Data Synthesis and Moderator Analyses

Intragroup change effect size (standardized mean difference) was calculated using the following formula:

$$d = \left(\frac{\overline{Y_1} - \overline{Y_2}}{S_{within}} \right)$$

where $\overline{Y_1}$ is the pretreatment sample mean, $\overline{Y_2}$ is the posttreatment sample mean, and S_{within}:

$$S_{within} = \frac{\sqrt{SD_1^2 + SD_2^2 - 2r \times SD_1 \times SD_2}}{\sqrt{2\,(1 - r)}}$$

where SD_1 is the standard deviation of the pretreatment sample mean, SD_2 is the standard deviation of the posttreatment sample mean, and r is the correlation between pretreatment and posttreatment scores.

For studies reporting difference in means, standard deviation of difference and sample size, the intragroup change effect size was calculated using the following formula:

$$d = \frac{\overline{Y_1}}{\left(\frac{SD_1}{\sqrt{2\,(1 - r)}} \right)}$$

where $\overline{Y_1}$ is the given paired difference in means, SD_1 is the given standard deviation of the paired difference, and r is the estimated correlation between pretreatment and posttreatment scores.

For studies reporting difference in means, confidence limits, sample size, and confidence level, the intragroup change effect size was calculated using the following formula:

$$d = \overline{Y_1} \times \sqrt{2 \times (1 - R)}$$

where $\overline{Y_1}$ is the standardized paired difference in means and R is the imputed R-value (given as 0.50).

Hedges g can be computed by multiplying d by correction factor:

$$J = 1 - \frac{3}{4df - 1}$$

where df is the degrees of freedom to estimate the intragroup standard deviation.

Q is determined by the following formula:

$$Q = \sum_{i=1}^{k} W_i Y_i^2 - \frac{\left(\sum_{i=1}^{k} W_i Y_i \right)^2}{\sum_{i=1}^{k} W_i}$$

with W_i being the weight of the study, Y_i the effect size of the study, and k the number of studies included. To determine the expected value of Q, we used the degrees of freedom (df = k − 1), with k being the number of studies included. A significant Q test (P value less than alpha set at 0.05) indicates heterogeneity in effect sizes.

We estimated the variance of the true effect between the studies (T^2) using the following formula:

$$T^2 = \frac{Q - df}{C}$$

where:

$$C = \sum W_i - \frac{\sum W_i^2}{\sum W_i}$$

I^2 is determined by using the following formula:

$$I^2 = \left(\frac{Q - df}{Q} \right) \times 100\%$$

I^2 is expressed as a ratio with a range of 0 to 100% and describes what proportion of the observed variance reflects real differences in effect sizes. Higgins and Thompson[1] suggest that values of 25%, 50%, and 75% can be considered as low, moderate, and high, respectively.

We computed the fail-safe N using the following formula:

$$X = \frac{K\,(K\overline{Z}^2 - 2.706)}{2.706}$$

where K is the number of studies in the meta-analysis and is $\overline{Z}$ the mean Z obtained from the K studies. The effect size can be considered to be robust if the required number of studies (X) to reduce the overall effect size to a nonsignificant level exceeds $5K + 10$.[2]

We used the Trim and Fill method, which examines whether negative or positive trials are overrepresented or underrepresented, accounting for the sample size. This information can then be used to recalculate the effect size estimates if the funnel plot is asymmetric. The divergence of the original effect size and the recalculated effect size reveal how robust the results are.

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Appendix C: Artikel 3

Psychophysiology

Conditioning of Amitriptyline-Induced REM-Sleep Suppression in Healthy Participants: A Randomized Controlled Trial

Journal:	*Psychophysiology*
Manuscript ID	Draft
Wiley - Manuscript type:	Original article
Date Submitted by the Author:	n/a
Complete List of Authors:	Winkler, Alexander; Philipps-University Marburg, Faculty of Psychology, Clinical Psychology Rheker, Julia; Philipps-University Marburg, Faculty of Psychology, Clinical Psychology Doering, Bettina; Philipps-University Marburg, Faculty of Psychology, Clinical Psychology Rief, Winfried; Philipps-University Marburg, Faculty of Psychology, Clinical Psychology
Keywords:	Conditioning < Content/Topics, Sleep < Content/Topics, Polisomnography < Methods, Pharmacology < Content/Topics

Conditioning of Amitriptyline-Induced REM-Sleep Suppression in Healthy Participants: A Randomized Controlled Trial

Running Title: Conditioning of Amitriptyline-Induced REM-Sleep Suppression

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Conflict of Interests

The authors declare no competing financial interests.

Acknowledgements

The study was prepared in the context of the FOR1328 research unit on placebo and nocebo mechanisms and was supported by a grant from the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG). We wish to thank Dr. Gudrun Schürmann for medical examinations and medical advice during the study.

Abstract

Clinical trials in sleep disorders report substantial improvement in symptoms in their placebo groups. Behavioral conditioning is one of the underlying mechanisms of the placebo response. However, we do not know whether and if so, the extent to which sleep architecture is influenced by behavioral conditioning, similarly to other physiological responses, i.e., those in the immune system. We therefore applied a conditioning paradigm to 39 healthy adults pairing a novel-tasting drink (conditioned stimulus, CS) with the REM-sleep suppressing tricyclic antidepressant amitriptyline as unconditioned stimulus (US) during the acquisition phase. Subsequent sole presentation of the CS (together with a placebo pill) in an evocation night led to significantly more REM-sleep in the amitriptyline group. Instead of the expected REM-sleep suppression in the evocation night, we observed more REM-sleep, indicating a conditioned drug-antagonistic response or rebound.

Significance Statement

Evidence from research over the past decade has demonstrated that a substantial proportion of the drug response in pharmacological treatments is attributable to the placebo response. Deeper understanding of the underlying mechanisms enables us to utilize the placebo response in clinical practice, reduce health care expenses, and optimize drug development. Since behavioral conditioning is suspected to be one of the underlying mechanisms of placebo responses in general and has been successfully investigated in other physiological systems, our study aims to apply the paradigm of behavioral conditioning using effects on sleep architecture as the objective outcome. We were unable to demonstrate that REM-sleep suppression triggered by amitriptyline is simply accessible to conditioning; we also address the effects that interfere with conditioning.

Introduction

Symptom improvement after pharmacologically inert treatment – the placebo response - is observed in most randomized controlled trials (RCTs) that attempt to differentiate the drug's specific pharmacologic effects from unspecific effects in the placebo group. RCTs have revealed substantial effects of placebo treatments in pain, depression, Parkinson's disease, irritable bowel syndrome, and sleep disorders (M. Schedlowski, Enck, Rief, & Bingel, 2015). Meta-analyses assessing the proportion of the placebo response relative to the drug response in RCTs reveal that placebo response rates account for up to 70% of symptom improvement in RCTs for depression (Kirsch & Sapirstein, 1998; Mora, Nestoriuc, & Rief, 2011; Rief et al., 2009) and up to 60% in RCTs for primary insomnia (Winkler & Rief, 2015). Better understanding of the underlying mechanisms is essential to utilizing the placebo response in clinical practice. Placebo-controlled dose reduction is just one conceivable clinical example of utilizing the placebo response to minimize side effects and health care expenses in pharmacological treatments (Doering & Rief, 2012). Understanding the placebo response is also essential to optimizing clinical trial designs in drug development (Enck, Bingel, Schedlowski, & Rief, 2013).

Our understanding of the mechanisms underlying the placebo response has grown substantially over the past decade (Enck et al., 2013). Associative learning (conditioning) processes are relevant mechanisms that contribute to the placebo response in addition to patients' expectations about treatment benefits and the quality and quantity of doctor-patient communication (Colloca, 2014; Colloca, Jonas, Killen, Miller, & Shurtleff, 2014; M. Schedlowski et al., 2015). In other words, the association between a certain pill and a specific therapeutic outcome can be conditioned and evoked by the context stimuli of drug intake. In pain therapy, for instance, a placebo pill is capable of inducing an opioid-mediated improvement in pain endurance similar to that of morphine after repetitive administrations of the active drug (Fabrizio Benedetti, Pollo, & Colloca, 2007). Classical conditioning seems to

be the key mechanism behind the placebo response, especially in physiological processes (F. Benedetti et al., 2003; Frisaldi, Piedimonte, & Benedetti, 2015; Pacheco-Lopez, Engler, Niemi, & Schedlowski, 2006; Riether et al., 2008; Manfred Schedlowski & Pacheco-López, 2010).

The typical paradigm to investigate the behavioral conditioning of pharmacological reactions is to pair a pharmacological agent (unconditioned stimulus/US) that produces physiological changes (unconditioned reaction/UR) with a novel stimulus such as a colored drink with an unknown taste (neutral stimulus). After multiple pairings in an acquisition phase, the neutral stimulus becomes a conditioned stimulus (CS). The physiological changes formerly induced by the US can be mimicked by the presentation of the CS alone in the subsequent evocation phase (Doering & Rief, 2012).

Human sleep offers us the intriguing opportunity to provide a proof of principle for the conditioning of pharmacological reactions as (1) sleep architecture can be altered by a pharmacological agent, (2) sleep is objectively measurable via polysomnographic recordings (PSG), (3) humans have no conscious expectations regarding neurophysiological processes during sleep, and (4) sleep is a physiological process. Current studies in placebo research have provided evidence of the conditioning of pharmacological reactions in healthy human subjects using the example of changes in immune (Goebel et al., 2002; Manfred Schedlowski & Pacheco-López, 2010; Wirth et al., 2011), endocrine (F. Benedetti et al., 2003), and respiratory (F. Benedetti, Amanzio, Baldi, Casadio, & Maggi, 1999) functions. The conditioning of changes in sleep architecture had not, to the best of our knowledge, been investigated before this investigation of ours.

To provide first proof of principle for the conditioning of changes in sleep architecture, we used the REM-sleep suppressing effect of amitriptyline in a classical conditioning paradigm. We hypothesized that participants taking amitriptyline would exhibit less REM-sleep in the third of four nights of medication intake (acquisition phase) than

participants taking a placebo pill. Furthermore, we hypothesized that, after having undergone the aforementioned acquisition phase and a three to four day washout phase with no pill intake, receiving a placebo would lead to less REM-sleep in the amitriptyline group than in the placebo group (evocation phase).

Methods

Participants

Forty healthy volunteers of both sexes were recruited between April and September 2014 via an advertisement in the Department of Psychology at the Philipps University of Marburg (Germany). Inclusion criteria were age between 18 and 69 years, no alcohol consumption and no driving throughout the study, regular sleeping habits, and fluency in German. All participants underwent a medical examination including interviews about their medical history, an electrocardiogram, blood tests, and a urine pregnancy test (in females only) by a physician trained in Good Clinical Practice (GCP). A trained psychologist also questioned them about their mental health status according to the International Diagnosis Checklists (Hiller, Zaudig, & Mombour, 2004). Exclusion criteria were contraindications to the study medication as mentioned in the information sheet for health professionals, allergies to any substances used in the study, pregnancy or nursing, suffering from a mental disorder or medical condition, taking any concomitant medication interfering with the study medication, participation in another clinical trial within the last three months, and being an employee of the principal investigator.

Participants were informed about the study procedure and potential side effects of the study medication before the study began. All participants gave written informed consent and were paid for their participation. The experiment was conducted according to the Declaration of Helsinki and registered at www.clinicaltrials.gov (identifier NCT02127736). The ethics committee of the National Physician Chamber Hessen (Landesärztekammer Hessen) approved the study protocol.

Study Medication

Participants in the drug group received amitriptyline on four consecutive nights in a 50 mg capsule for oral application together with 100ml of a novel-tasting drink (lychee juice with woodruff syrup and blue food coloring). Amitriptyline is a tricyclic antidepressant

approved for the treatment of depressive disorders and chronic pain often used as an off-label treatment in sleep disorders.

A well-known effect of amitriptyline at a dose of 50mg is that it reliably suppresses up to 50% of REM-sleep (Doerr et al., 2010; Mayers & Baldwin, 2005; Winokur et al., 2001). The novel-tasting drink functioned to increase the distinctiveness and saliency of the pharmaceutical form in order to enhance its suitability for conditioning and influence the magnitude of the conditioned reaction, as summarized by Doering and Rief (2012).

Outcome Measures

Our primary outcome measure was the proportion of REM-sleep on total sleep time (REM%TST) assessed via polysomnographic recordings (PSG) at three time points (baseline-, acquisition-, and evocation-night). Total sleep time (TST), sleep period time (SPT), sleep efficiency (SE), sleep onset latency (SOL), wake after sleep onset (WASO) as well as the latency, duration and proportion on TST in each sleep stage (N1, N2, N3 and REM) were assessed via PSG as secondary outcome measures.

Ambulatory PSG (via Embla® Titanium PSG device and Embla® RemLogic™ Software; Kanata, Embla Systems, Natus Medical Inc.) encompassed (a) electroencephalographic recordings (EEG; 256Hz, high-pass filter 0.3Hz, low-pass filter 35Hz) from F3, C3, O1, F4, C4, O2, Cz referenced to the linked mastoids M1 and M2, (b) left and right electrooculography (EOG; 256Hz, high-pass filter 0.3Hz, low-pass filter 14Hz) from EOG-L and EOG-R, and (c) submental surface electromyography (EMG; 256Hz, high-pass filter 10Hz) from Chin-L, Chin-R, and Chin-M. Electrodes were placed according to the international 10-20 system (Committee on methods of clinical examination in electroencephalography, 1958). Maximum electrode impedance was 5 kΩ.

Sleep recordings were scored manually (by epochs of 30s length) according to the 2007 American Academy of Sleep Medicine (AASM) scoring manual (Iber, Ancoli-Israel, Chesson, & Quan, 2007) by an experienced medical technical assistant blinded to group

allocation. Study medication was well tolerated. Detailed analyses of side effects are analyzed and reported elsewhere (J. Rheker, A. Winkler, B. K. Doering, and W. Rief, unpublished observations).

Behavioral Protocol

After their medical and psychological examinations, participants were randomly assigned to one of two groups (amitriptyline or identically looking placebo) by an independent experienced scientist not associated with the reported trial. Investigators and participants were blinded to group allocation (medication was given in sequentially numbered medication containers) until data collection was completed. Two days before the baseline assessment, all participants spent an adaptation night getting used to sleeping with the device attached. Sleep was measured at baseline via PSG with no experimental manipulation.

As displayed in Figure 1, participants assigned to the amitriptyline group underwent a classical conditioning paradigm with amitriptyline. During the acquisition phase (nights one to four), participants received 50mg of amitriptyline (unconditioned stimulus = US) together with 100ml of a novel-tasting drink (neutral stimulus = NS, which is supposed to became the conditioned stimulus = CS). Participants were instructed to take the medication together with the novel-tasting drink 30 minutes before going to bed. Sleep was measured via PSG on day three of the acquisition phase. The acquisition phase was followed by a three to four day washout phase (nights five to seven or eight; the washout phase's duration varied for organizational reasons). In the following evocation night, participants were re-exposed to the same novel-tasting drink (CS) together with a placebo pill. Sleep was again assessed that night via PSG. This behavioral protocol was based on trials on conditioned immunosuppression (Goebel et al., 2002; Wirth et al., 2011).

Participants assigned to the placebo control group underwent the same procedure; however, they received placebo pills instead of amitriptyline during the acquisition phase, as shown in Figure 1.

Statistical Analysis

Statistical analyses were performed with IBM SPSS Statistics 21.0 for Windows (Chicago, SPSS, Inc.). Baseline sample characteristics were analyzed using independent sample t-tests and chi-square-tests. Baseline sleep characteristics were analyzed using a multivariate analysis of variance (MANOVA) to test for baseline differences between groups. To test for differences in the primary outcome variable (REM%TST), we conducted the analysis of variance (ANOVA) for repeated measures using *time* (baseline, acquisition, and evocation) as the repeated factor and *group* (amitriptyline or placebo) as the between-group factor. Bonferroni-corrected post-hoc tests assessed group differences at specific time points if the ANOVA revealed a significant overall group x time interaction. In case data was missing (consequence of a technical breakdown of the PSG device after a few minutes of recording), that particular night's data was excluded from the analyses.

Results

Forty participants were recruited and randomly assigned to the amitriptyline and the placebo group. In the amitriptyline group, one participant discontinued study participation during the acquisition phase because of side effects, leaving 19 subjects in the amitriptyline group and 20 subjects in the placebo group for our analysis. We observed no significant differences in sample characteristics (age, sex, body weight, and body-mass-index) as shown in Table 1, or in sleep parameters obtained by PSG between participants of the two groups at baseline (MANOVA: $F(15, 22) = 0.86$, $p = .610$).

While the groups did not differ in their proportion of REM-sleep at baseline, they did differ at acquisition and the evocation night, as demonstrated by a significant interaction effect between time and group ($F(2, 32) = 32.92$, $p < .001$) in the ANOVA for repeated measures. As Table 2 illustrates, participants in the amitriptyline group exhibited less REM-sleep at the end of the acquisition phase and more REM-sleep at the evocation night than placebo-group participants, as demonstrated by pairwise comparisons. As Figure 2 reveals, we noted more REM-sleep rather than the expected REM-sleep suppression in the amitriptyline group compared to the placebo group during the evocation night.

Discussion

As hypothesized, the amitriptyline group showed significantly less REM-sleep after three nights of pill intake (acquisition phase) than the placebo group, indicating that the intended amitriptyline-induced REM-sleep suppression had succeeded. Contrary to our hypothesis that receiving a placebo in the evocation night would lead to less REM-sleep in the amitriptyline group, they revealed significantly more REM-sleep than the placebo group.

This is an intriguing result, since several studies examining the conditioning of pharmacological reactions (e.g.Goebel et al., 2002; Stockhorst et al., 2004; Wirth et al., 2011) have reported that learned drug-agonistic responses are retrievable by CS exposure alone after a repeated contingent pairing of a taste stimulus (CS) together with administration of a pharmacological agent.

In our opinion, there are four explanations for this result. (1) The first explanation is that the conditioning succeeded in an unintended way, namely that a drug-antagonistic response of the body after amitriptyline intake had been conditioned instead of the reduction in REM-sleep itself. This interpretation concurs with findings by M. A. Flaten, Simonsen, Waterloo, and Olsen (1997), who reported a drug-antagonistic conditioned response in a pharmacological conditioning paradigm using a muscle relaxant to decrease blink reflex amplitude and duration in healthy volunteers. It also corresponds with earlier reviews on drug conditioning paradigms (Eikelboom & Stewart, 1982; Magne Arve Flaten, 2009; Ramsay & Woods, 1997) postulating that CS exposure may generate physiological responses that resemble the observed drug effect (agonistic response) or in a direction opposite to that of the observed drug effect (antagonistic response) in activating homeostatic mechanisms (Magne Arve Flaten, 2009). (2) Since this is the first attempt to examine conditioning changes in sleep architecture, it is possible that amitriptyline-induced REM-sleep suppression is not susceptible to behavioral conditioning. One possible reason for that could be the time delay of several hours between US and UR, as well as the complex nature of the UR (several changes in

physiological parameters). (3) Rebound may have taken place even after a three to four day washout, indicating a long-lasting physiological impact of a relatively low dose of amitriptyline on sleep architecture. However, this is unlikely considering the 10-38 hours elimination half-life. (4) Although we based our behavioral protocol on conditioning paradigms of neuroendocrine and immune functions (Albring et al., 2012; Goebel et al., 2002; Kirschbaum et al., 1992; Wirth et al., 2011), another explanation is that our attempt to condition either failed or was too weak to compete against rebound effects for reasons of methodology (e.g. an inappropriate number of acquisition/evocation nights, disadvantageous duration of the washout phase, or an ineffective stimulus).

Several limitations of this study need to be addressed: the current literature does not yet clarify whether paradigms of neuroendocrine and immune functions can be applied to modulating sleep architecture in general. It took only one evocation night for us trying to recall the learned REM-sleep reduction, a potential problem since there is evidence that a single re-exposure to the conditioned stimulus might not suffice to evoke learned immunosuppression (Albring et al., 2012) in healthy participants. Moreover, we may have implemented a relatively short acquisition phase with only four days, another possible problem since Colloca, Petrovic, Wager, Ingvar, and Benedetti (2010) found that an increase in the number of associations during the acquisition phase resulted in more persistent placebo responses.

The generalizability of our findings is limited to healthy adults. Future studies should assess patients (who may also be better placebo responders than healthy volunteers) presenting sleep disorders like primary insomnia to apply the knowledge of conditioning as a placebo mechanism to a clinically more relevant population.

Variation in the duration of the washout phase (three or four days) for organizational reasons compromised our study's internal validity. To examine a potential bias, we tested for

differences in the primary outcome variable between those participants who spent three days of washout and those who spent four days of washout and detected no significant differences.

Since it was unclear whether conditioning paradigms of neuroendocrine and immune functions also apply to the modulation of sleep architecture, future studies should vary in effect all aspects of the conditioning paradigms (number and duration of acquisition, washout and evocation nights) to optimize the current behavioral conditioning protocol in general.

Our results may also have been influenced by psychological, physiological and neurobiological predictors of conditioned placebo responses. Participants can differ in their ability to learn placebo effects, a factor essential to consider when implementing learning protocols in clinical practice (Wendt, Albring, & Schedlowski, 2014). M. Schedlowski et al. (2015) provide an overview of individual predisposition for placebo responses like anxiety, hypnotic suggestibility, locus of control, self-efficacy, plasma noradrenaline level, and genetic traits.

Our study is an initial step to apply knowledge about behavioral conditioning to the example of changes in sleep architecture. We assumed that sleep is more affected by conditioning as a source of learning, while the participants' conscious expectation (in association with the proportion of REM-sleep) may play a minor role. We were inspired to conduct this study because of the substantial placebo effects demonstrated in clinical trials addressing insomnia (Winkler & Rief, 2015). While simple conditioning does not seem to explain these effects, more complex influences (e.g. conditioning of the drug-antagonistic response) could be involved.

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Conflict of Interests
The authors declare no competing financial interests.

Acknowledgements

The study was prepared in the context of the FOR1328 research unit on placebo and nocebo mechanisms and was supported by a grant from the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG). We wish to thank Dr. Gudrun Schürmann for medical examinations and medical advice during the study.

Tables

Table 1 Sample characteristics

Characteristics	Amitriptyline group (n=19)	Placebo group (n=20)	Group Differences
Age in years, M (SD)	24.4 (3.5)	23.6 (3.7)	t(37) = -0.71, p = .481
Number females, n (%)	11 (57.9%)	11 (55.0%)	$\chi^2(1) = 0.03$, p = .556
Weight in kg, M (SD)	67.5 (11.3)	63.9 (9.0)	t(36) = -1.09, p = .285
BMI, M (SD)	22.8 (1.8)	21.5 (2.2)	t(36) = -1.95, p = .059

Note. BMI = Body-Mass-Index; n = Number of participants; M = Mean; SD = Standard deviation.

Table 2 REM Sleep as Percentage of Total Sleep Time (REM%TST): group comparisons

	Placebo group		Amitriptyline group		Mean Difference	SE	Confidence Interval	p
	M	SEM	M	SEM				
Baseline	0.192	0.012	0.220	0.013	-0.028	.018	-0.065; 0.008	.127
After acquisition	0.226	0.010	0.129	0.011	0.097	.015	0.067; 0.127	.000
After evocation	0.218	0.010	0.249	0.010	-0.032	.014	-0.061; -0.003	.033

Note. REM%TST = REM sleep as percentage of total sleep time; M = Mean; SEM = Standard error of the mean.

Figure Captions and Figures

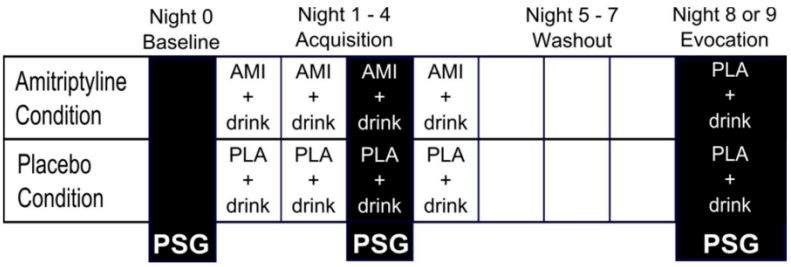

Figure 1. Behavioral conditioning paradigm (see Methods for details); AMI = 50mg amitriptyline; drink = novel-tasting drink; PLA = placebo; PSG = polysomnographic recording.

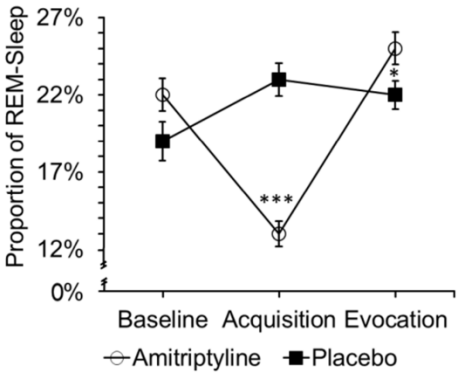

Figure 2. Proportion of REM-sleep on total sleep time for the amitriptyline and placebo condition at baseline, acquisition and evocation (see Results for details). Bonferroni-corrected post-hoc t-tests ***p<0.001; **p< .01; *p< 0.05. Data are shown as M ± SEM (standard error of the mean).

Highlights

- Behavioral conditioning of REM-sleep suppression was applied for the first time.
- The Placeboresponse was not simply explainable by conditioning.
- Significant evidence for a conditioned drug-antagonistic response was found.

Appendix D: Tabellarischer Lebenslauf und Publikationen

(Der Lebenslauf ist nicht Teil der Veröffentlichung)

Appendix E: Eidesstattliche Erklärung

Hiermit versichere ich, dass ich meine Dissertation „Placeboeffekte in der pharmakologischen Behandlung von Insomnie“ selbst und ohne fremde Hilfe verfasst habe. Ich habe keine anderen als die angegebenen Quellen und Hilfsmittel genutzt und alle vollständig oder sinngemäß übernommenen Zitate als solche gekennzeichnet. Die Dissertation wurde weder in der vorliegenden noch in einer ähnlichen Form bei einer anderen in- oder ausländischen Hochschule anlässlich eines Promotionsgesuchs oder zu anderen Prüfungszwecken eingereicht.

Marburg (Lahn), im Februar 16 Alexander J. Winkler