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BEHANDLUNGSERWARTUNGEN IM KONTEXT PHARMAKOLOGISCHER UND PSYCHOLOGISCHER INTERVENTIONEN

Einfluss auf positive und negative Behandlungsergebnisse

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1 Zusammenfassung und Abstract

1.1 Zusammenfassung

Sowohl in Bezug auf positive als auch auf negative Ergebnisse von Interventionen zur Behandlung verschiedener Störungen und Erkrankungen wird den Behandlungserwartungen eine wichtige Rolle zugeschrieben. Dies gilt zum einen im Bereich der Pharmakotherapie, zum anderen aber auch im Bereich der Psychotherapie (Amanzio, Corazzini, Vase, & Benedetti, 2009; Constantino, Arnkoff, Glass, Ametrano, & Smith, 2011; Rief et al., 2015; Schedlowski, Enck, Rief, & Bingel, 2015). Trotz vielfältiger Forschung in diesen Bereichen bleiben einige Fragen ungeklärt.

In der Pharmakotherapie ist bislang noch nicht erforscht, welche Rolle Lernerfahrungen als ein Mechanismus, über den Behandlungserwartungen gebildet werden können, beim Auftreten von Nebenwirkungen spielen. Aus diesem Grund wurde in der ersten Studie dieser publikationsbasierten Dissertation untersucht, ob die typischen Nebenwirkungen eines trizyklischen Antidepressivums durch klassisches Konditionieren gelernt werden können. Die Ergebnisse der Studie legen nahe, dass Lernmechanismen eine wichtige Rolle beim erneuten Auftreten von Nebenwirkungen durch Antidepressiva spielen.

Bei neueren psychologischen Interventionen wie beispielsweise internetbasierten Selbsthilfeprogrammen konnte bislang noch nicht eindeutig nachgewiesen werden, ob Erwartungen den Behandlungserfolg beeinflussen. In einer zweiten Studie wurde in einem internetbasierten Selbsthilfeprogramm für Patienten, die unter Tinnitus leiden, regressionsanalytisch untersucht, ob die vor Interventionsbeginn gemessenen Erwartungen an die Behandlung einen Einfluss auf das Hauptbehandlungsergebnis (Beeinträchtigung durch den Tinnitus) haben. Es konnte gezeigt werden, dass Erwartungen in Form von Hoffnung auf Besserung vor Therapiebeginn ein signifikanter Prädiktor für größere Symptomverbesserung durch das Selbsthilfeprogramm waren.

Bei negativen Effekten, die durch Psychotherapie auftreten, ist bislang die Rolle der Behandlungserwartungen nicht erforscht, auch gibt es generell wenig empirische Studien zu Auftretenshäufigkeiten, -arten und Ursachen von negativen Effekten von Psychotherapie. In einer dritten Studie sollte deshalb zunächst untersucht werden, welche Ursachen Patienten für die negativen Effekte von Psychotherapie sehen. Hierfür wurde eine qualitative Interviewstudie durchgeführt, in der vier Hauptbereiche als Ursachen gefunden werden konnten: *Gründe für Erfolglosigkeit oder Nebenwirkungen einer angemessenen Therapie*, *Probleme in der therapeutischen Beziehung*, *Gründe für Erfolglosigkeit oder Nebenwirkungen durch unprofessionelle Ausübung der Behandlung* und *Schädigung durch unethisches Verhalten des Therapeuten*. Die vierte Studie widmete sich dann der Fragestellung, ob die Erwartungen an die Behandlung die nach einer Therapie berichteten negativen Effekte von Psychotherapie beeinflussen. Auch in dieser Studie konnte die vor Therapiebeginn gemessene Hoffnung auf Besserung der Patienten als signifikanter Prädiktor für die nach der Therapie berichteten negativen Effekte der Patienten gefunden werden. Mehr Hoffnung auf Besserung führte zu weniger berichteten negativen Effekten.

Die im Rahmen der Dissertation durchgeführten Studien unterstreichen die Wichtigkeit von Behandlungserwartungen sowohl im Kontext pharmakologischer als auch psychologischer Interventionen und ihren Einfluss auf positive und negative Effekte von Behandlungen.

1.2 Abstract

Treatment expectations are known to play an important role with regard to positive and negative effects of pharmacological and psychological interventions (Amanzio et al., 2009; Constantino et al., 2011; Rief et al., 2015; Schedlowski et al., 2015). Although research in this field is growing fast, some aspects remain unclear.

In pharmacological treatments it has not yet been examined whether prior experience, representing one important mechanism responsible for treatment expectations, influences the occurrence of side effects. The first study of this thesis aimed at examining whether an antidepressant's side effects can be learned via classical conditioning. Our results strongly suggest that learning plays an important role in the reoccurrence of an antidepressant's side effects.

The impact of treatment expectations on the intervention's outcome is yet unclear for more recently developed psychological interventions, such as internet-based self-helps. In the second study, we examined whether treatment expectations influence the main outcome (tinnitus distress) in an internet-based self-help for patients suffering from tinnitus. We found that pre-treatment expectations in the form of hope of improvement are a significant predictor for symptom improvement.

When it comes to negative effects of psychotherapy, so far the role of treatment expectations has not been sufficiently examined and studies on incidence, origins, and types of negative effects are generally rare. Therefore, in a third study, we aimed at investigating what origins patients hold responsible for the occurrence of negative effects. In a qualitative interview study we were able to determine four main categories to which the negative effects could be attributed: *reasons for negative effects of an appropriate therapy*, *problems in the therapeutic relationship*, *reasons for negative effects due to unprofessionally performed therapy*, and *malpractice and unethical behavior*. In the fourth study, we investigated whether the negative effects that are reported by the

patients after psychotherapy are influenced by treatment expectations. Again, we found that expectations in the form of hope of improvement were a significant predictor for negative effects of psychotherapy in the direction that more hope of improvement led to less negative effects.

The studies conducted within this thesis underline the importance of treatment expectations within pharmacological and psychological interventions and their influence on positive and negative treatment outcomes.

2 Hintergrund

2.1 Erwartungen im Kontext von Behandlungen

Erwartungen sind Annahmen über die Wahrscheinlichkeit, dass ein Ereignis oder Ergebnis eintreten wird (Price, Finniss, & Benedetti, 2008). Im Kontext von therapeutischen Interventionen oder Behandlungen konnten die Erwartungen bezüglich des Behandlungsergebnisses als einer der stärksten Prädiktoren für den Behandlungserfolg gefunden werden (Rief & Glombiewski, 2016). Neben dem Einfluss von Erwartungen auf ein positives Behandlungsergebnis konnte allerdings auch herausgefunden werden, dass Erwartungen einen Effekt auf negative Behandlungsergebnisse wie beispielsweise Nebenwirkungen oder einen reduzierten positiven Behandlungseffekt haben (Benedetti, Lanotte, Lopiano, & Colloca, 2007; Bingel et al., 2011; Colloca & Miller, 2011).

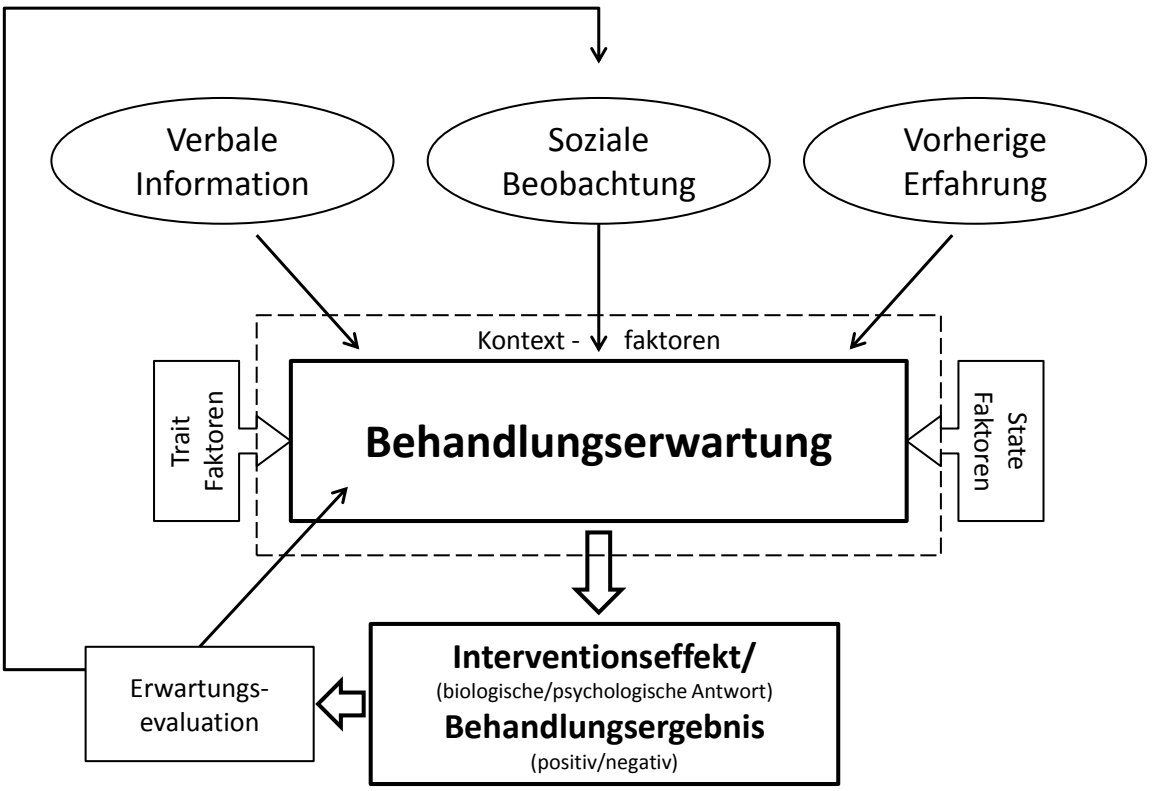

Abbildung 1. Ein Modell zu Erwartungen im Kontext von Behandlungen nach Bingel, Schedlowski, Rief & Büchel, 2016 (unveröffentlichte Daten)
Verbale Informationen, soziale Beobachtung und vorherige Erfahrungen können zur Ausbildung von Behandlungserwartungen beitragen. Darüber hinaus werden Behandlungserwartungen auch durch Kontext- sowie State- und Trait-Faktoren des Individuums beeinflusst. Das Behandlungsergebnis wird schließlich evaluiert und beeinflusst über eine Feedbackschleife zukünftige Behandlungserwartungen.

Wie Abbildung 1 verdeutlicht, können Behandlungserwartungen durch verschiedene Faktoren gebildet und beeinflusst werden. Als ein wesentlicher Mechanismus, der zur Ausbildung von Erwartungen führt, konnten verbale Informationen identifiziert werden (Cohen, 2014; Crichton, Dodd, Schmid, Gamble, & Petrie, 2013; Mondaini et al., 2007; Witthöft & Rubin, 2013). Hiermit sind beispielsweise die Kommunikation mit dem medizinischen Personal, die schriftliche Aufklärung durch Patienteninformationen, aber auch Informationen, die durch Medien vermittelt werden, gemeint. Darüber hinaus kann auch soziale Beobachtung zur Ausbildung von Erwartungen führen (Colloca & Benedetti, 2009; Vögtle, Barke, & Kröner-Herwig, 2013). Beobachtet ein Patient beispielsweise, dass eine Psychotherapie bei einer Freundin gut gewirkt hat, können sich darüber positive Erwartungen an den Erfolg der eigenen Therapie herausbilden. Ein weiterer wichtiger Mechanismus, der zur Ausbildung von Behandlungserwartungen führt, sind vorherige Erfahrungen oder Lernen bzw. klassisches Konditionieren (Kessner, Wiech, Forkmann, Ploner, & Bingel, 2013; Stewart-Williams & Podd, 2004). Hatte ein Patient bereits eine positive Vorerfahrung mit einem bestimmten Medikament, beeinflusst dies seine zukünftige Erwartung an das Medikament. In der Pharmakotherapie wird in diesem Zusammenhang auch von der Konditionierung pharmakologischer Reaktionen gesprochen (Doering & Rief, 2012). Neben den bereits beschriebenen Mechanismen werden die Behandlungserwartungen noch durch weitere Faktoren beeinflusst. Ein Faktor ist der therapeutische Kontext (Blasi, Harkness, Ernst, Georgiou, & Kleijnen, 2001; Kaptchuk et al., 2008). Dies kann sich auf das Gebäude oder den Raum beziehen, in dem die Behandlung stattfindet, aber auch auf das Auftreten des medizinischen Personals oder die Art und Weise, in der eine Behandlung verabreicht wird. Wie in dem Modell dargestellt ist, können auch Faktoren des Individuums wie beispielsweise eine generelle Ängstlichkeit oder eine momentane Ängstlichkeit die Behandlungserwartungen beeinflussen (Price et al., 2008). Schließlich werden die Behandlungserwartungen auch mittels einer Feedbackschleife durch eine Evaluation des Behandlungsergebnisses beeinflusst.

2.2 Behandlungserwartungen in der Pharmakotherapie

2.2.1 Placebo- und Noceboeffekte

Im Rahmen pharmakologischer Behandlungen bezeichnet man als Placebo eine Tablette ohne Wirkstoff, welche in Arzneimittelstudien häufig für den Vergleich mit dem Verum (der eigentlichen Tablette mit Wirkstoff) eingesetzt wird (Benedetti, 2008). Auf diese Weise soll der individuelle Effekt des Verums an der Behandlung identifiziert werden (Enck, Bingel, Schedlowski, & Rief, 2013). Aus diesen Studien ist bekannt, dass häufig ein substantieller Anteil der Symptomverbesserung bereits in den Placebogruppen auftritt (Kirsch & Sapirstein, 1998; Winkler & Rief, 2015), eine Wirkung, die Placeboeffekt genannt wird (Schedlowski et al., 2015). Ebenso ist aus den Placebogruppen von Medikamentenstudien bekannt, dass die von den Patienten berichteten Nebenwirkungen häufig den Nebenwirkungen in der Verumgruppe entsprechen (Amanzio et al., 2009; Rief et al., 2009). In diesem Fall spricht man vom sogenannten Noceboeffekt (Colloca & Miller, 2011). Sowohl bei Placebo- als auch bei Noceboeffekten werden die Erwartungen als der Hauptmechanismus für deren Wirkung angenommen (Colloca, 2014; Schwarz, Pfister, & Büchel, 2016). Wie bereits zuvor beschrieben, können diese Erwartungen sich durch unterschiedliche Mechanismen ausbilden und durch verschiedene Faktoren beeinflusst werden (s. 2.1 Erwartungen im Kontext von Behandlungen).

Zu betonen ist, dass Placebo- und Noceboeffekte nicht nur im Rahmen einer Placebobehandlung auftreten, sondern auch einen substantiellen Anteil am Ergebnis von Behandlungen mit Verum haben (Bingel et al., 2011). Darüber hinaus sind Placebo- und Noceboeffekte nicht auf pharmakologische Behandlungen beschränkt, sondern können auch im Rahmen jeglicher anderer Therapien, z.B. bei Operationen oder Akupunktur, auftreten (Linde, Jürgens, Hammes, Weidenhammer, & Melchart, 2005; Sihvonen et al., 2013).

2.2.3 Konditionieren pharmakologischer Reaktionen

Wie bereits zuvor beschrieben, ist ein Mechanismus, über den Erwartungen gebildet werden, Vorerfahrung oder Lernen. In der Pharmakotherapie bedeutet dies beispielsweise, dass eine positive Vorerfahrung mit einem Medikament dazu führt, dass die Erwartungen an die Wirksamkeit dieses Medikamentes steigen, was künftig einen weiteren Einfluss auf die Wirksamkeit des Medikamentes haben kann. Eine Form von Vorerfahrung kann durch Konditionieren gebildet werden. Ein Mechanismus, der sich auch in der Pharmakotherapie zu Nutze gemacht werden kann (Doering & Rief, 2012). Beim sogenannten Konditionieren pharmakologischer Reaktionen wird üblicherweise ein pharmakologischer Wirkstoff (unkonditionierter Stimulus = US), der eine bestimmte physiologische Reaktion, die unkonditionierte Reaktion (UR), hervorruft, mit einem neutralen Stimulus (NS) wie beispielsweise einem neuartig schmeckenden Getränk gepaart verabreicht. Während der Akquisitionsphase werden US und NS mehrfach gemeinsam mit dem Ziel verabreicht, dass der NS zum konditionierten Stimulus (CS) wird. Um zu überprüfen, ob der NS zum CS geworden ist und nun die gleichen physiologischen Reaktionen (konditionierte Reaktion = CR) hervorruft wie ursprünglich der US, wird in der sogenannten Evokation anstelle des US, also des pharmakologischen Wirkstoffes, ein Placebo in gleicher Darreichungsform gepaart mit dem CS verabreicht (s. Abbildung 2).

Die Konditionierung solcher pharmakologischer Reaktionen konnte in ersten Studien z.B. für Immunreaktionen (Albring et al., 2012; Goebel, Meykadeh, Kou, Schedlowski, & Hengge, 2008) und das endokrine System (Benedetti et al., 2003) nachgewiesen werden. In diesen Studien wurde immer auf die Hauptwirkung des Medikamentes fokussiert, nicht aber auf mögliche Nebenwirkungen des Medikamentes. Aber auch für das Auftreten von Nebenwirkungen wird angenommen, dass Vorerfahrung oder Lernmechanismen eine Rolle spielen (Amanzio, 2015). Ein Beispiel, anhand dessen sich dieser Effekt demonstrieren lässt, ist Übelkeit, die Krebspatienten als Nebenwirkung der Chemotherapie erleben (Matteson, Roscoe, Hickok, &

Morrow, 2002). Es kann vorkommen, dass ein ursprünglich neutraler Stimulus wie der Raum, in dem die Therapie stattfindet, irgendwann dazu führt, dass dem Patienten bereits beim Betreten des Raumes übel wird (Matteson et al., 2002).

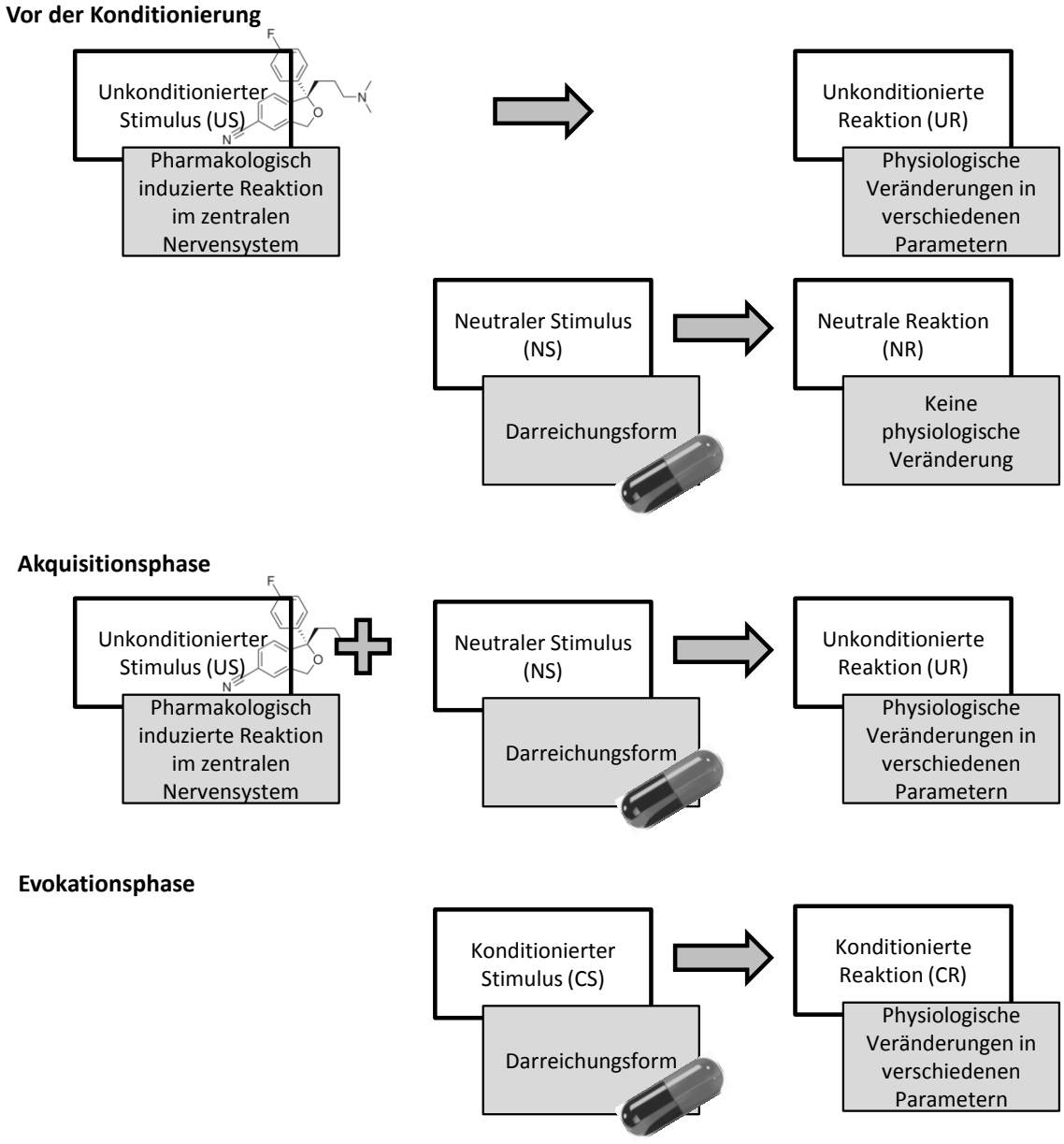

Abbildung 2. Konditionieren pharmakologischer Reaktionen
Klassisches Konditionieren mit pharmakologischen Stimuli nach Doering & Rief, 2012. In der Akquisitionsphase wird ein ursprünglich neutraler Stimulus wie die Darreichungsform eines Medikamentes mit einem pharmakologischen Wirkstoff gepaart, der zu bestimmten physiologischen Veränderungen führt. Nach mehrmaligem Paaren der beiden Stimuli kann die Darreichungsform alleine die physiologischen Veränderungen hervorrufen.

In ersten experimentellen Paradigmen konnte außerdem bereits nachgewiesen werden, dass Noceboeffekte im Zusammenhang mit Bewegungsübelkeit und Hyperalge-

sie gelernt werden können (Colloca, Petrovic, Wager, Ingvar, & Benedetti, 2010; Colloca, Sigaudo, & Benedetti, 2008; Klosterhalfen et al., 2009). Bei diesen Noceboeffekten handelt es sich jedoch nicht um die Nebenwirkungen eines Medikamentes und somit nicht um konditionierte pharmakologische Reaktionen. Ein experimenteller Nachweis, ob die Nebenwirkungen eines Medikamentes auch durch klassisches Konditionieren gelernt werden, steht noch aus.

2.3 Behandlungserwartungen in der Psychotherapie

2.3.1 Erwartungen als Einflussfaktor für den Erfolg von psychologischen Behandlungen

In der Diskussion um die Wirkfaktoren von Psychotherapie wurde postuliert, dass der Behandlungserfolg neben spezifischen Interventionen auch auf sogenannte allgemeine Wirkfaktoren zurückgeführt werden kann (Lambert & Kleinstäuber, 2016; Lambert & Ogles, 2004; Lambert, 2005). Zu diesen allgemeinen Wirkfaktoren zählen unter anderem die Erwartungen an eine Behandlung, die auch als Faktor für den Behandlungserfolg bestätigt werden konnten (Constantino et al., 2011; Greenberg, Constantino, & Bruce, 2006; Lambert, 2005). Neuere Ansätze legen außerdem nahe, dass die Psychotherapie sich mehr auf Erwartungen konzentrieren sollte (Rief & Glombiewski, 2016; Rief et al., 2015). Während der Einfluss von Erwartungen auf ein positives Behandlungsergebnis in der klassischen Psychotherapie also bereits bestätigt wurde, stellt sich die Frage, welche Rolle Erwartungen in neueren Anwendungsformen von psychologischen Behandlungen spielen.

Internetbasierte Selbsthilfeprogramme. Es gibt immer mehr Studien und Metaanalysen, die die Effektivität von sogenannten internetbasierten Selbsthilfeprogrammen belegen (Carlbring, Westling, Ljungstrand, Eskelius, & Andersson, 2001; Cuijpers, Straten, & Andersson, 2008; Hesser et al., 2012; Spek et al., 2007). Für diese Programme gibt es keine einheitliche Definition. Da die Vorreiter dieser Programme in Schweden zu finden sind (Andersson, 2009), soll in der vorliegenden Arbeit auch

eine Definition benutzt werden, die sich auf das so gennannte „Schwedische Modell" bezieht. Demzufolge werden internetbasierte Behandlungsprogramme definiert als eine Behandlung, die auf Selbsthilfebüchern oder –manualen basieren und von einem Therapeuten begleitet werden, der Rückmeldungen gibt und Fragen beantwortet. Der Kontakt zwischen Patient und Therapeut findet normalerweise per E-Mail zu festgelegten Zeitpunkten statt und ähnelt somit dem therapeutischen Kontakt in traditionellen Therapien. Die gesamte Behandlung sowie die E-Mail-Kommunikation erfolgt in der Regel über eine Behandlungsplattform, von der die Patienten die entsprechenden Behandlungsmodule herunterladen können. Die Behandlung kann somit auch anonym stattfinden (Andersson et al., 2008).

Obwohl die Wirksamkeit dieser Programme vielfältig belegt wurde (Andersson, 2016), ist nach wie vor nicht geklärt, welche Wirkfaktoren diese Programme so effektiv machen. Ein angenommener Wirkfaktor ist die therapeutische Unterstützung. Während minimale therapeutische Unterstützung von manchen Forschern als eine Mindestanforderung für die Wirksamkeit von internetbasierten Behandlungsprogrammen postuliert wird (Andersson, Carlbring, Berger, Almlöv, & Cuijpers, 2009; Carlbring, Andersson, & Kaldo, 2011) und in Metaanalysen und Reviews gezeigt werden konnte, dass Programme mit therapeutischer Unterstützung denen ohne Unterstützung überlegen sind (Baumeister, Reichler, Munzinger, & Lin, 2014; Johansson & Andersson, 2012; Spek et al., 2007), zeigen andere Studien, dass trotz nicht vorhandener therapeutischer Unterstützung gute Behandlungsergebnisse erzielt werden können (Hirai & Clum, 2005; Klein & Richards, 2001). In den entsprechenden Studien gibt es jedoch teilweise hohe Abbrecherraten (Farvolden, Denisoff, Selby, Bagby, & Rudy, 2005), dementsprechend handelt es sich um sehr selektive Stichproben und die Ergebnisse können nicht generalisiert werden. Darüber hinaus stellt sich die Frage, ob es zwingend notwendig ist, dass die therapeutische Unterstützung nach einem vorher festgelegten Plan erfolgt, oder ob eine therapeutische Unterstützung, die nach individuellem Bedarf der Patienten angeboten wird, auch wirksam ist. Erste Hinwei-

se sprechen dafür, dass diese Form der therapeutischen Unterstützung effektiv ist (Berger et al., 2011). Für ein breiteres Verständnis über die Rolle der therapeutischen Unterstützung als ein Wirkfaktor für internetbasierte Behandlungsprogramme sollte diese umfassender untersucht werden.

Da in klassischen Psychotherapien die Erwartungen an den Behandlungserfolg als ein Einflussfaktor für den tatsächlichen Therapieerfolg identifiziert werden konnten (Constantino et al., 2011; Greenberg et al., 2006), ist es naheliegend, zu untersuchen, ob diese auch in internetbasierten Selbsthilfeprogrammen eine Rolle spielen. Bisherige Studien, die die Rolle von Erwartungen im Zusammenhang mit internetbasierten Therapien untersucht haben, führen zu gemischten Ergebnissen (Boettcher, Renneberg, & Berger, 2013; Hedman et al., 2012, 2013; Jasper et al., 2014; Kaldo, Levin, Widarsson, & Buhrman, 2008). Während die Erwartungen in einigen Studien einen signifikanten Einfluss auf den Erfolg der Behandlung hatten (Boettcher et al., 2013; Hedman et al., 2012), konnte in anderen Studien keine Prädiktion des Behandlungserfolgs durch Erwartungen erfolgen (Hedman et al., 2013; Jasper et al., 2014). Die bisherigen Studien haben Erwartungen meist mithilfe der *Credibility-* oder *C-Scale* erfasst (Borkovec & Nau, 1972; Devilly & Borkovec, 2000). Als *Credibility* wird eine Form der Erwartung bezeichnet, die sich darauf bezieht, wie sehr angenommen wird, dass die Behandlung den eigenen Bedürfnissen entspricht (Constantino et al., 2011). Dies wird häufig als ein Konstrukt mit den Erwartungen an das Behandlungsergebnis zusammengefasst. Auch in der *Credibility-* oder *C-Scale* ist dies bei der Auswertung häufig der Fall. Allerdings argumentieren manche Autoren, dass verschiedene Konstrukte von Erwartungen besser getrennt betrachtet und erfasst werden sollten (Greenberg et al., 2006; Schulte, 2008). Das heißt, dass neben der unklaren Rolle der therapeutischen Unterstützung in internetbasierten Selbsthilfeprogrammen auch die Rolle von Behandlungserwartungen im Zusammenhang mit dem Behandlungserfolg noch nicht hinreichend untersucht wurde.

2.3.2 Erwartungen als Einflussfaktor auf negative Effekte von Psychotherapie

Neben der Erforschung der Effektivität von Psychotherapie beschäftigt sich die Forschung mittlerweile auch vermehrt mit negativen Effekten von psychologischen Interventionen (Boettcher, Rozental, Andersson, & Carlbring, 2014; Crawford et al., 2016; Ladwig, Nestoriuc, & Rief, 2014; Moritz et al., 2015; Rozental, Boettcher, Andersson, Schmidt, & Carlbring, 2015). Obwohl das Wissen um mögliche negative Effekte von Psychotherapie bereits seit langer Zeit besteht (Barlow, 2010) und der sogenannte *deterioration effect*, d.h. die Verschlechterung der Symptomatik durch Psychotherapie, bereits in den 1960er Jahren als ein negativer Effekt von Psychotherapie postuliert wurde (Bergin, 1966), wurde dieses Thema in den nachfolgenden Jahrzehnten nur wenig untersucht. Erst in jüngerer Zeit rückte das Thema mehr und mehr in den Fokus von Forschern, welche sich zunächst insbesondere mit der Definition und Klassifizierung von negativen Effekten von Psychotherapie beschäftigt haben (Hoffmann, Rudolf, & Strauß, 2008; Kaczmarek et al., 2012; Lieberei & Linden, 2008; Linden, 2013). Während die Definition von Nebenwirkungen oder unerwünschten Ereignissen in der Pharmakotherapie eindeutig geregelt ist, gibt es hierfür in der Psychotherapie keine einheitliche Definition (Linden, 2013). Manche Autoren sprechen im Zusammenhang mit negativen Effekten von Psychotherapie zum Beispiel von Symptomverschlechterung, Therapie-Non-Response, unerwünschten Ereignissen, unethischem Therapeutenverhalten oder Nebenwirkungen (Bergin, 1966; Hoffmann et al., 2008; Linden, 2013; Mohr & Francisco, 1995). In der vorliegenden Arbeit soll eine relativ breite Definition für negative Effekte von Psychotherapie verwendet werden: Als negative Effekte von Psychotherapie werden Veränderungen in allen Bereichen des Wohlbefindens eines Patienten beschrieben, die von dem Patienten als negativ wahrgenommen werden und ihm direkt oder indirekt schaden. Diese Veränderungen können während oder nach der Psychotherapie auftreten und die Ursache für diese Veränderungen wird von den Patienten in der Psychotherapie gesehen. Wenn die negativen Effekte nicht auf ein Fehlverhalten des Therapeuten zurückzuführen sind, können diese auch als *Nebenwirkungen* bezeichnet werden. Ist

jedoch von einem Fehlverhalten des Therapeuten auszugehen, kann von *Fehlverhalten und unethischem Verhalten* gesprochen werden (vgl. Ladwig et al., 2014; Linden, 2013). Im Sinne dieser Definition können negative Effekte beispielsweise bedeuten, dass sich die Symptomatik der Patienten durch die Therapie verschlechtert. Es kann auch bedeuten, dass Probleme in Partnerschaften oder Freundschaften der Patienten auftreten, da diese durch die Therapie gelernt haben, ihre eigenen Bedürfnisse vermehrt zu äußern. Probleme mit Versicherungen oder Angst vor Stigmatisierung sind weitere Beispiele für negative Effekte von Psychotherapie. Nimmt der Therapeut Patienten nicht ernst oder wendet falsche Therapietechniken an, würde nach oben beschriebener Definition von therapeutischem Fehlverhalten gesprochen.

Obwohl die Forschung sich mittlerweile vermehrt mit dem Thema negativer Effekte von Psychotherapie auseinandersetzt, sind empirische Studien zu dem Thema noch rar. Erste Ergebnisse legen nahe, dass Patienten nach Psychotherapien von einem substantiellen Anteil negativer Effekte berichten, die auf die Therapie zurückführbar sind (Crawford et al., 2016; Ladwig et al., 2014; Moritz et al., 2015). Allerdings schwanken die Häufigkeiten je nach Studie stark. Während in einer groß angelegten englischen Studie die Häufigkeit von längerfristigen negativen Effekten mit 5,2% angegeben wird (Crawford et al., 2016), zeigte sich in deutschen Stichproben, dass ungefähr 93% der Psychotherapiepatienten von mindestens einem negativen Effekt in einem Lebensbereich berichten (Ladwig et al., 2014; Moritz et al., 2015). Die großen Unterschiede zwischen den Studien könnten an unterschiedlichen Definitionen und Erhebungsmethoden von negativen Effekten liegen. In jedem Fall machen sie deutlich, dass im Bereich der negativen Effekte von Psychotherapie noch mehr Forschung notwendig ist. Dementsprechend gibt es auch noch nicht viele Ergebnisse über mögliche Einflussfaktoren auf negative Effekte von Psychotherapie. Insbesondere im Hinblick auf Erwartungen liegt bislang erst ein Ergebnis vor, das nahelegt, dass nicht erfüllte Patientenerwartungen an die Therapie zu mehr negativen Effekten führen (Ladwig et al., 2014).

3 Darstellung des Dissertationsvorhabens

3.1 Relevanz und Herleitung der Fragestellungen

Behandlungserwartungen konnten als einer der wichtigsten Prädiktoren für den Erfolg von Behandlungen gefunden werden (Rief et al., 2015). Sowohl bei pharmakologischen Therapien als auch bei psychologischen Interventionen steht außer Frage, dass Behandlungserwartungen den Behandlungserfolg beeinflussen (Benedetti, 2008; Bingel et al., 2011; Colloca, 2014; Constantino et al., 2011). Dennoch gibt es in den verschiedenen Bereichen weiteren Forschungsbedarf, um durch die Klärung noch offener Fragen Behandlungen weiter zu verbessern und zu optimieren.

In der Pharmakotherapie konnten bereits Vorerfahrungen oder Konditionierung als ein wichtiger Mechanismus identifiziert werden, über den Behandlungserwartungen in diesem Kontext gebildet werden; dies konnte insbesondere im Hinblick auf die gewünschten Effekte eines Medikaments nachgewiesen werden (Albring et al., 2012; Goebel et al., 2008). Es ist jedoch noch ungeklärt, inwiefern die Nebenwirkungen eines Pharmakons gelernt werden können und somit das erneute Auftreten dieser Nebenwirkungen bei wiederholter Einnahme des Pharmakons beeinflussen können. Da Nebenwirkungen neben anderen Faktoren ein Grund für fehlende Adhärenz bei der Medikamenteneinnahme sind (De las Cuevas, Peñate, & Sanz, 2014; Hung, Wang, Liu, Hsu, & Yang, 2011), ist eine Erforschung der Mechanismen, die zu Nebenwirkungen führen, von besonderer Wichtigkeit. Insbesondere bei Antidepressiva konnte nachgewiesen werden, dass Nebenwirkungen zu verminderter Adhärenz führen (Ashton, Jamerson, Weinstein, & Wagoner, 2005; Murata & Kanbayashi, 2012; Serna, Cruz, Real, Gascó, & Galván, 2010). Daher sollte in der ersten Fragstellung dieser Dissertation untersucht werden, ob die spezifischen Nebenwirkungen eines trizyklischen Antidepressivums durch klassisches Konditionieren gelernt und anschließend wieder abgerufen werden können. Da es sich um einen ersten Machbarkeitsnachweis handelt, sollten gesunde Probanden untersucht werden.

In der klassischen Psychotherapie wurde bereits vielfältig belegt, dass Erwartungen ein Einflussfaktor für Therapieerfolg sind (Constantino et al., 2011). In neueren therapeutischen Behandlungsmethoden wie internetbasierten Selbsthilfetrainings, welche sich als effektiv für die Behandlung verschiedenster psychischer Störungen erwiesen (Cuijpers et al., 2008; Spek et al., 2007), gibt es jedoch noch keine konsistenten Befunde über den Einfluss von Behandlungserwartungen auf den Erfolg dieser Interventionen (Boettcher et al., 2013; Hedman et al., 2012, 2013; Jasper et al., 2014). Um die Rolle der Erwartungen in diesen neuen Behandlungsformen genauer zu untersuchen, soll ein Programm, das sich bereits als erfolgreich erwiesen hat, verwendet werden. Für die Beeinträchtigung, die Patienten durch Tinnitus entsteht, konnte bereits in verschiedenen Studien die Effektivität eines internetbasierten Selbsthilfeprogramms belegt werden (Hesser et al., 2012; Jasper et al., 2014). Aus diesem Grund sollte im Rahmen der zweiten Fragestellung dieser Dissertation untersucht werden, wie sich Behandlungserwartungen auf den Behandlungserfolg – das heißt eine verringerte Beeinträchtigung durch den Tinnitus – eines etablierten internetbasierten Behandlungsprogramms für Tinnituspatienten auswirken. Darüber hinaus sollte die bislang ungeklärte Rolle der therapeutischen Unterstützung in internetbasierten Selbsthilfetrainings für Tinnituspatienten untersucht werden. Die Untersuchung dieser Fragstellungen ist ein wichtiger Schritt, um internetbasierte Behandlungsprogramme weiter zu verbessern.

Neben den positiven Effekten von Psychotherapie fokussiert die Forschung immer mehr auch auf negative Effekte von Psychotherapie (Barlow, 2010; Linden, 2013; Mohr & Francisco, 1995). Empirische Studien in diesem Bereich sind jedoch rar und bislang ist nicht ausreichend untersucht worden, was die Ursachen für diese negativen Effekte sein können. Um ein tieferes Verständnis für negative Effekte von Psychotherapie zu bekommen, sollte deshalb zunächst mittels einer qualitativen Interviewstudie untersucht werden, was die Ursachen für negative Effekte von Psychotherapie sind. Auch gibt es erst wenige Studien, die die Auftretenshäufigkeiten nega-

tiver Effekte von Psychotherapie untersucht haben (Crawford et al., 2016; Ladwig et al., 2014; Moritz et al., 2015). Dementsprechend gibt es auch noch keine Studien, die den Einfluss von Behandlungserwartungen, die Patienten vor Therapiebeginn berichten, auf die nach der Therapie angegebenen negativen Effekte von Psychotherapie untersucht haben. Somit sollten in einer weiteren Studie zunächst mögliche Unterschiede im Auftreten negativer Effekte von Psychotherapie in unterschiedlichen Kliniksettings erforscht werden. In einem nächsten Schritt sollte untersucht werden, welchen Einfluss die Erwartungen an die Behandlung auf das Auftreten von negativen Effekten von Psychotherapie haben.

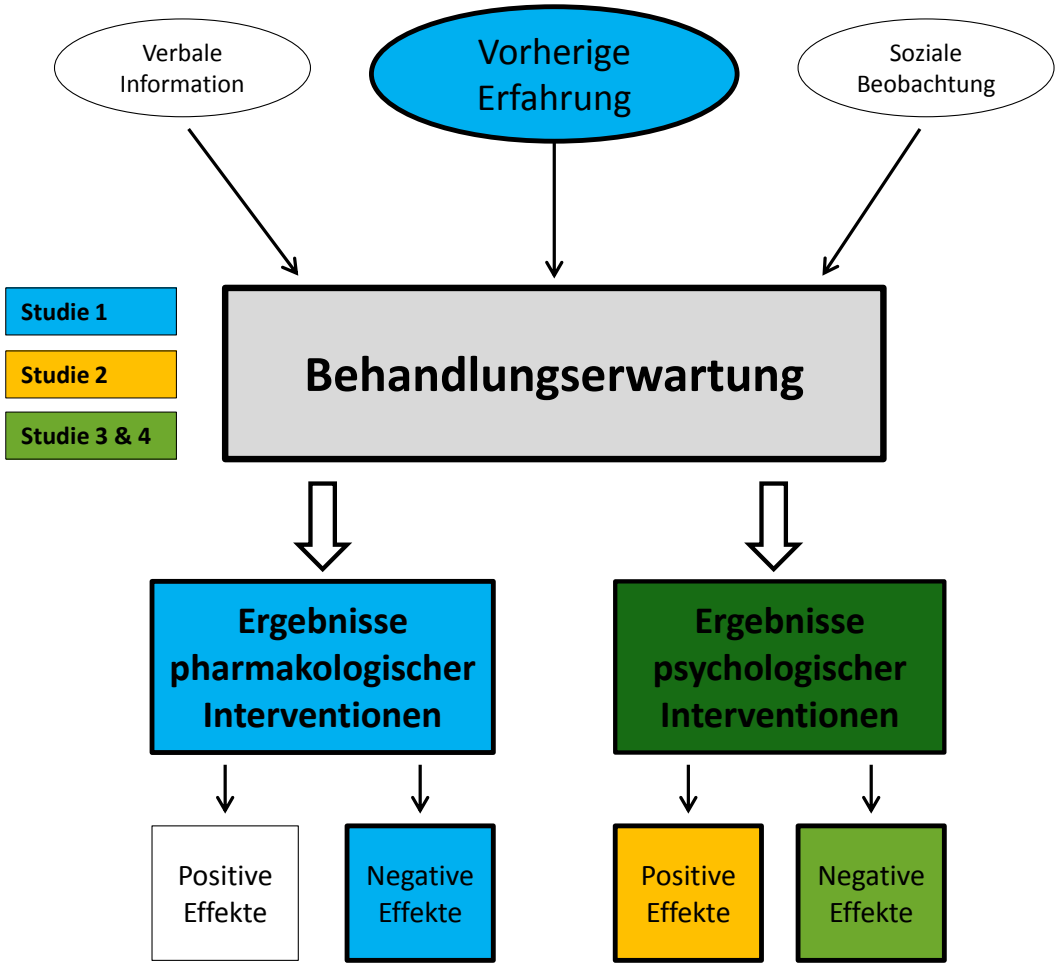

Abbildung 3. Erwartungen im Kontext von Behandlungen – Abwandlung des Modells aus Abb. 1
In dem Modell ist dargestellt mit welchen Teilen des Modells zu Behandlungserwartungen sich die vorliegende Dissertation beschäftigt. Studie 1 untersucht den Einfluss vorheriger Erfahrungen auf das Auftreten von Nebenwirkungen bei pharmakologischen Interventionen. Studie 2 beschäftigt sich mit der Rolle von Behandlungserwartungen im Kontext positiver Effekte von psychologischen Interventionen und Studie 3 und 4 mit den entsprechenden negativen Effekten dieser Interventionen.

3.2 Fragestellungen und Ziele des Dissertationsvorhabens

Ausgehend vom bisherigen Forschungsstand zur Rolle der Erwartungen in pharmakologischen und psychologischen Interventionen sollen im vorliegenden Dissertationsvorhaben drei Fragestellungen untersucht werden (s. auch Abb. 3):

(1) Welche Rolle spielen Erwartungen in Form von Lernmechanismen bei der Entwicklung von Nebenwirkungen in der Pharmakotherapie **(Studie 1)**?
    - Es soll untersucht werden, ob die spezifischen Nebenwirkungen des trizyklischen Antidepressivums Amitriptylin durch klassisches Konditionieren gelernt werden können.

(2) Welche Rolle spielen Erwartungen für den Behandlungserfolg von internetbasierten Therapieprogrammen **(Studie 2)**?
    - Es soll untersucht werden, wie sich Behandlungserwartungen auf den Erfolg eines internetbasierten Selbsthilfeprogramms für Patienten, die unter Beeinträchtigungen durch ihren Tinnitus leiden, auswirken.

(3) Welche Rolle spielen Erwartungen bei der Entwicklung von negativen Effekten von Psychotherapie?
    - Zunächst soll mittels Patienteninterviews durch eine qualitative Inhaltsanalyse untersucht werden, was die Ursachen für negative Effekte von Psychotherapie sind **(Studie 3)**.
    - Es soll untersucht werden, ob Behandlungserwartungen einen Einfluss auf die Anzahl an berichteten negativen Effekten von Psychotherapie haben **(Studie 4)**.

4 Zusammenfassung der Studien

4.1 Studie 1: Der Einfluss von Erwartungen in Form von Lernmechanismen auf das Auftreten von Antidepressiva-Nebenwirkungen

Rheker, J., Winkler, A., Doering, B.K., & Rief, W. (submitted). Learning to experience side effects after antidepressant intake – Results from a randomized, controlled, double-blind study. Manuscript submitted for publication in *Psychopharmacology*

Hintergrund. Nebenwirkungen sind ein wichtiger Grund für Non-Compliance bei der Einnahme von Antidepressiva (De las Cuevas et al., 2014; Hung et al., 2011; Murata & Kanbayashi, 2012). Diesbezügliche Studien zeigen, dass die Aufklärung über Nebenwirkungen bestimmte Erwartungen hervorrufen kann, welche dann zu Nebenwirkungen führen können (Cohen, 2014; Mondaini et al., 2007; Nestoriuc, Orav, Liang, Horne, & Barsky, 2010). Zudem wird angenommen, dass vorherige Erfahrungen oder Lernprozesse das Auftreten von Nebenwirkungen beeinflussen (Amanzio, 2015). Allerdings wurden genaue Zusammenhänge hierzu bisher unzureichend erforscht. In dieser Studie untersuchen wir deshalb, ob die spezifischen Nebenwirkungen eines Antidepressivums durch klassisches Konditionieren gelernt werden können.

Methode. Die gesunden Probanden (n = 39) wurden zufällig einer von zwei Gruppen (Experimentalgruppe und Kontrollgruppe) zugeteilt. Alle Probanden durchliefen ein klassisches Konditionierungsparadigma. Während der Akquisitionsphase (Lernphase) erhielten die 19 Probanden der Experimentalgruppe das trizyklische Antidepressivum Amitriptylin. Die 20 Probanden der Kontrollgruppe erhielten eine identisch aussehende Tablette ohne Wirkstoff (Placebo). Die Tabletten wurden an vier aufeinanderfolgenden Nächten eingenommen. Die Tabletteneinnahme erfolgte immer in Kombination mit einem neuartig schmeckenden Getränk. Nach einer Auswasch-Phase erhielten Probanden beider Gruppen ein Placebo zusammen mit dem neuartig schmeckenden Getränk (Evokation). Nebenwirkungen wurden mit der Generic Assessment of Side Effects Scale (GASE; Rief, Barsky, Glombiewski, Nestoriuc, & Glaesmer, 2010) vor der Akquisition (Baseline), nach der Akquisition und nach der

Evokation erfasst. Um die für das eingenommene Antidepressivum spezifischen Nebenwirkungen zu erfassen, wurde ein Antidepressiva-spezifischer Score berechnet. Hierfür wurden die Symptom-Items, die nach der Akquisition mindestens 50% der Probanden in der Experimentalgruppe berichteten, ausgewählt. Dies sind mit Mundtrockenheit, Schwindel/Benommenheit, Kreislaufschwierigkeiten/niedriger Blutdruck und Erschöpfung/Antriebslosigkeit Symptome, die auch im Physician's Desk Reference (Barnhart, 1988) als typische Nebenwirkungen von Amitriptylin angegeben sind.

Ergebnisse. Verglichen mit der eigenen Baseline und der Placebo-Kontrollgruppe, berichteten Probanden der Experimentalgruppe signifikant mehr Antidepressiva-spezifische Nebenwirkungen nach der Akquisition ($p \leq .001$; Effektstärke Hedge's g = 1.56; 95% Konfidenzintervall (KI): 0.84 – 2.28). Auch nach der Evokation, in der alle Probanden ein Placebo erhielten, berichteten die Probanden der Experimentalgruppe, die die klassische Konditionierung mit Amitriptylin durchlaufen hatten, signifikant mehr Antidepressiva-spezifische Nebenwirkungen als die Probanden der Kontrollgruppe, die nie Amitriptylin eingenommen hatten (p = .045; g = 0.66; KI: 0.01 – 1.30).

Diskussion. Die spezifischen Nebenwirkungen eines Antidepressivums können durch ein Konditionierungsparadigma gelernt und im Anschluss durch ein Placebo hervorgerufen werden. Die Ergebnisse legen nahe, dass Lernmechanismen eine Rolle bei der Entstehung von Nebenwirkungen von Antidepressiva spielen. Für die Verschreibung von Antidepressiva impliziert dies, dass es sinnvoll ist, die Vorerfahrungen eines Patienten mit einem bestimmten Antidepressivum zu erfragen, bevor dieses verschrieben wird. Um diese ersten Hinweise weiter empirisch zu untermauern, sollten zukünftige Studien insbesondere Patienten mit Depressionen untersuchen.

4.2 Studie 2: Die Rolle von Behandlungserwartungen und therapeutischer Unterstützung in einem internetbasierten Selbsthilfeprogramm für Tinnitus-Patienten

Rheker, J., Andersson, G., & Weise, C. (2015). The role of “on demand” therapist guidance vs. no support in the treatment of tinnitus via the internet: A randomized controlled trial. *Internet Interventions*, *2*(2), 189–199. http://doi.org/10.1016/j.invent.2015.03.007

Hintergrund. Internetbasierte kognitiv-verhaltenstherapeutische Selbsthilfeprogramme erwiesen sich als erfolgreich in der Behandlung von Beeinträchtigungen, die durch Tinnitus entstehen (Hesser et al., 2012; Jasper et al., 2014). Allerdings ist bislang erst wenig über die zugrunde liegenden Mechanismen bekannt, die internetbasierte Behandlungsangebote erfolgreich machen. Es wird angenommen, dass das Vorhandensein von zumindest minimaler therapeutischer Unterstützung wichtig für den Erfolg internetbasierter Behandlungen ist (Baumeister et al., 2014). Es ist jedoch unklar, wie viel therapeutische Unterstützung mindestens notwendig ist, um ein gutes Behandlungsergebnis zu erzielen (Andersson et al., 2009; Palmqvist, Carlbring, & Andersson, 2007). In traditioneller Psychotherapie konnte festgestellt werden, dass positive Erwartungen an die Therapie den Behandlungserfolg positiv beeinflussen können (Constantino et al., 2011). Bezüglich internetbasierter Selbsthilfeprogramme ist der Einfluss von Erwartungen auf den Behandlungserfolg jedoch bisher unzureichend untersucht. Ziel der Studie war es deshalb zu untersuchen, wie sich therapeutische Unterstützung, die bei Bedarf angefordert werden kann, im Vergleich zu keiner Unterstützung auf den Therapieerfolg eines internetbasierten Selbsthilfeprogramms für Tinnitus auswirkt. Darüber hinaus sollte untersucht werden, ob positive Behandlungserwartungen den Erfolg der Behandlung vorhersagen können.

Methode. Insgesamt wurden 112 Tinnitus-Patienten randomisiert einer von zwei Gruppen (therapeutische Unterstützung bei Bedarf oder keine therapeutische Unterstützung) zugeordnet. Beide Gruppen erhielten ein etabliertes internetbasiertes kognitiv-verhaltenstherapeutisches Behandlungsprogramm für Tinnitus (Jasper et al., 2014). Das Programm wurde den Patienten über eine eigens für die Studie erstellte passwortgeschützte Website dargeboten. Nach einem individuell erstellten Behandlungsplan wurden den Teilnehmern wöchentlich neue Inhalte freigeschaltet. Die Pa-

tienten der einen Gruppe (n=56) konnten bei Bedarf eine Therapeutin um Unterstützung bitten. Die therapeutische Unterstützung fand ausschließlich per E-Mail statt. Die Patienten der anderen Gruppe (n=56) erhielten keine therapeutische Unterstützung. Tinnitus-Beeinträchtigung wurde vor und nach der Behandlung mit dem Tinnitus Handicap Inventory (THI; Newman, Jacobson, & Spitzer, 1996) und dem Mini-Tinnitus Fragebogen (Mini-TF; Hiller & Goebel, 2004) gemessen. Erfolgserwartungen wurden vor Behandlungsbeginn mit dem Patientenfragebogen zur Therapieerwartung und Therapieevaluation (PATHEV; Schulte, 2005) gemessen.

Ergebnisse. Nach Behandlungsende wurde im Vergleich zum Behandlungsbeginn signifikant weniger Beeinträchtigung durch den Tinnitus in der Gruppe mit therapeutischer Unterstützung (THI: $t(55) = 7.51$, $p \leq .001$, Mini-TQ: $t(55) = 8.24$, $p \leq .001$) und in der Gruppe ohne therapeutische Unterstützung (THI: $t(55) = 7.68$, $p \leq .001$, Mini-TQ: $t(55) = 8.46$, $p \leq .001$) berichtet. Es konnten keine signifikanten Gruppenunterschiede oder Interaktionen festgestellt werden. Die Skala *Hoffnung auf Besserung* des PATHEV konnte eine signifikant verringerte Tinnitus-Beeinträchtigung (gemessen durch den THI) vorhersagen ($\beta = 0.28$, $p = .027$).

Diskussion. Die Ergebnisse zeigen, dass das internetbasierte Selbsthilfeprogramm eine gute Behandlungsalternative für Patienten, die unter Tinnitus leiden, ist und zwar unabhängig davon, ob therapeutische Unterstützung angeboten wird oder nicht. Da therapeutische Unterstützung immer als wichtiger Wirkmechanismus internetbasierter Behandlungen postuliert wurde (Carlbring et al., 2011), wirkt dieses Ergebnis auf den ersten Blick etwas überraschend. Vorherige Studien konnten jedoch auch keine einheitlichen Ergebnisse in Bezug auf therapeutische Unterstützung in internetbasierten Behandlungen erzielen (Baumeister et al., 2014; Berger et al., 2011). Insgesamt legen die Ergebnisse nahe, dass die Rolle therapeutischer Unterstützung in internetbasierten Behandlungsprogrammen noch genauer untersucht werden sollte. Darüber hinaus zeigen unsere Ergebnisse die Wichtigkeit von Erwartungen in Form von Hoffnung auf Besserung für den Behandlungserfolg in internetbasierten Selbsthilfeprogrammen für Tinnitus-Patienten. Für zukünftige internetbasierte Be-

handlungsprogramme bedeutet dies, dass es vorteilhaft sein kann, vor Behandlungsbeginn die Erwartungen der Patienten an die Behandlung zu optimieren.

4.3 Studie 3: Bereiche von negativen Effekten von Psychotherapie und Ursachen für deren Entstehung

Ladwig, I., Rheker, J., Rief, W., & Nestoriuc, Y (submitted). Patients' attributions regarding negative effects of psychotherapy: Qualitative interviews with an affected group. Manuscript submitted for publication in *Psychotherapy Research*

Hintergrund. Negative Effekte von Psychotherapie können in unterschiedlichen Bereichen auftreten und auch in ansonsten erfolgreichen Therapien (Ladwig et al., 2014). Es wurden verschiedene Versuche unternommen, die negativen Effekte von Psychotherapie zu definieren und zu kategorisieren (Kaczmarek et al., 2012; Lieberei & Linden, 2008; Linden, 2013). Auch bezüglich der Ursachen negativer Effekte von Psychotherapie wurde bereits ein Kategorisierungsversuch unternommen (Hoffmann et al., 2008). Dieser wurde jedoch noch nicht empirisch überprüft. In der aktuellen Studie sollen daher mittels Patienteninterviews zunächst Lebensbereiche, in denen negative Effekte von Psychotherapie auftreten, identifiziert werden und anschließend Ursachen für deren Entstehung exploriert werden.

Methode. Patienten, die negative Erfahrungen mit Psychotherapie gemacht haben, wurden mittels eines Interviews zu ihren Erfahrungen mit einer vorangegangen Psychotherapie befragt. Das Interview wurde basierend auf dem Inventar zur Erfassung negativer Effekte von Psychotherapie (Ladwig et al., 2014) entwickelt und umfasste sowohl offene als auch geschlossene Fragen. Die Interviews von 24 Patienten wurden transkribiert und mit der qualitativen Inhaltsanalyse (Mayring, 2010) ausgewertet. Es wurden Kategorien für zugrundeliegende ähnliche Inhalte entwickelt und in zwei Kategoriensystemen zusammengefasst: Ein System umfasst Lebensbereiche, in denen negative Effekte von Psychotherapie aufgetreten sind, das andere umfasst Ursachen von negativen Effekten. Häufigkeiten der Nennungen pro Kategorie wurden quantitativ ausgewertet.

Ergebnisse. Insgesamt wurden 127 negative Effekte berichtet, die in 15 Kategorien zusammengefasst werden konnten. Für die Ursachen dieser Effekte konnten vier Hauptkategorien mit verschiedenen Subkategorien identifiziert werden. Von den vier Hauptkategorien wurde *Gründe für Erfolglosigkeit oder Nebenwirkungen einer an-*

gemessenen Therapie 131 Mal als Ursache für negative Effekte angegeben. *Probleme in der therapeutischen Beziehung* wurde 76 Mal als Ursache genannt, *Gründe für Erfolglosigkeit oder Nebenwirkungen durch unprofessionelle Ausübung der Behandlung* wurde 58 Mal genannt und *Schädigung durch unethisches Verhalten des Therapeuten* 34 Mal.

Diskussion. Negative Effekte von Psychotherapie treten in verschiedenen Lebensbereichen der Patienten auf. Sie treten außerdem aufgrund therapeutischen Fehlverhaltens, aber auch in *lege artis* Therapien auf. Zukünftige Studien sollten herausfinden, welche dieser negativen Effekte verhindert werden können und welche als Teil des therapeutischen Prozesses gesehen werden müssen.

4.4 Studie 4: Die Rolle von Behandlungserwartungen im Zusammenhang mit negativen Effekten von Psychotherapie

Rheker, J., Beisel, S., Kräling, S., Rief, W. (submitted). Different treatment settings reveal various rates of negative effects of psychotherapy: Exemplifying the need to evaluate negative effects of psychotherapy by comparing a psychiatric to a psychosomatic hospital. Manuscript submitted for publication in *Psychiatry Research*

Hintergrund. Obwohl die Forschung sich vermehrt mit negativen Effekten von Psychotherapie beschäftigt (Barlow, 2010; Mohr & Francisco, 1995; Rozental et al., 2014), gibt es nur wenige Studien, die die Auftretenshäufigkeit dieser Effekte untersucht haben (Buckley, Karasu, & Charles, 1981; Crawford et al., 2016; Ladwig et al., 2014; Moritz et al., 2015). Diese Studien zeigen ein inkonsistentes Bild bezüglich der Häufigkeiten von negativen Effekten. Unterschiede können möglicherweise an verschiedenen Definitionen, Stichproben oder Erhebungsmethoden liegen. Darüber hinaus gibt es kaum Studien, die Faktoren untersucht haben, die möglicherweise das Auftreten von negativen Effekten der Psychotherapie begünstigen. Das Ziel der Studie war es aus diesem Grund zunächst zu untersuchen, ob in einer Psychiatrie im Vergleich zu einer psychosomatischen Rehabilitationsklinik eine andere Anzahl und eine andere Art von negativen Effekten von Psychotherapie auftreten. Des Weiteren sollte untersucht werden, ob Erwartungen an die Behandlung einen Einfluss auf das Auftreten von negativen Effekten von Psychotherapie haben.

Methode. Patienten wurden in einer psychosomatischen Rehabilitationsklinik (n = 93) und in einer Psychiatrie (n = 63) rekrutiert. Vor Behandlungsbeginn erhielten die Patienten einen Fragebogen, der neben demografischen Angaben und Fragen zu Vorerfahrungen mit Psychotherapie den Patientenfragebogen zur Therapieerwartung und Therapieevaluation (PATHEV; Schulte, 2005) enthielt. Zum Abschluss der Therapie in der Klinik erhielten die Patienten einen Abschlussfragebogen, in dem negative Effekte der Therapie mit dem Inventar zur Erfassung negativer Effekte von Psychotherapie (INEP; Ladwig et al., 2014) erhoben wurden. Aus den ersten 15 Items

des INEP wurde ein Summenscore gebildet, indem die von den Patienten auf die Therapie attribuierten negativen Effekte aufsummiert wurden.

Ergebnisse. Patienten aus der Psychiatrie berichteten im Mittel 1,41 negative Effekte und 58,7% aller Patienten berichteten mindestens einen negativen Effekt erlebt zu haben. In der psychosomatischen Stichprobe wurden im Mittel 0,76 negative Effekte berichtet. Von den Patienten berichteten 45,2% mindestens einen negativen Effekt erlebt zu haben. Die Unterschiede in berichteten negativen Effekten zwischen den Kliniken sind signifikant ($t(94.54) = -2.76$, $p = .007$). Die negativen Effekte, die in beiden Kliniken am häufigsten berichtet wurden, stimmen zwischen den Kliniken überein. Eine hierarchische lineare Regression über beide Kliniken hinweg ergab, dass über das Kliniksetting hinaus Erwartungen in Form von Hoffnung auf Besserung ein signifikanter Prädiktor für die berichteten negativen Effekte sind. Patienten, die weniger Hoffnung auf Besserung an die Therapie haben, berichten mehr negative Effekte der Therapie.

Diskussion. Die Ergebnisse zeigen, dass es notwendig ist, negative Effekte von Psychotherapie in verschiedenen Settings und Stichproben zu untersuchen, um in Bezug auf verschiedene Patientengruppen und Therapien adäquate Nutzen-Risiko-Verhältnisse zu berechnen. Darüber hinaus zeigte sich, dass Patienten mit weniger Hoffnung auf Besserung mehr negative Effekte der Therapie berichten. Dies könnte bedeuten, dass Interventionen, die auf eine Steigerung der Hoffnung auf Besserung vor Therapiebeginn abzielen, die negativen Effekte reduzieren könnten.

5 Zusammenfassende Diskussion und Ausblick

In der vorliegenden Arbeit ist es gelungen zu zeigen, dass Behandlungserwartungen sowohl in der Pharmakotherapie als auch bei psychologischen Behandlungen und sowohl im Hinblick auf das gewünschte Behandlungsergebnis als auch im Hinblick auf das Auftreten von unerwünschten Effekten der Behandlung eine Rolle spielen. Die im Rahmen dieser Dissertation durchgeführten Studien konnten das Wissen über Behandlungserwartungen an entscheidenden Stellen erweitern. In Studie 1 konnte erstmalig experimentell gezeigt werden, dass Lernerfahrungen das Auftreten von Nebenwirkungen durch Antidepressiva beeinflussen. Das Experiment zeigte, dass Probanden, die zuvor vier Mal Amitriptylin gepaart mit einem neuartig schmeckenden Getränk eingenommen hatten, nach der Einnahme eines Placebos gepaart mit dem neuartig schmeckenden Getränk zu einem substantiellen Anteil die gleichen Nebenwirkungen berichteten wie nach der Einnahme des Antidepressivums. Aus vorherigen Studien ist bereits bekannt, dass Behandlungserwartungen eine entscheidende Rolle im Hinblick auf das Auftreten von Nebenwirkungen in der Pharmakotherapie spielen (Amanzio et al., 2009), der spezifische Einfluss von Lernerfahrungen wurde in diesem Kontext jedoch noch nicht untersucht. Somit konnte unsere erste Studie einen wichtigen Beitrag für ein besseres Verständnis der zugrunde liegenden Mechanismen bei Nebenwirkungen von Antidepressiva leisten.

Der Einfluss von Behandlungserwartungen für den Erfolg von Psychotherapie steht außer Frage (Constantino et al., 2011; Greenberg et al., 2006), es konnte jedoch noch nicht eindeutig geklärt werden, ob Behandlungserwartungen auch in neueren psychologischen Interventionen wie internetbasierten Selbsthilfeprogrammen und im Hinblick auf das Auftreten von negativen Effekten von Psychotherapie eine Rolle spielen. In der 2. Studie konnte gezeigt werden, dass auch in internetbasierten Selbsthilfeprogrammen Behandlungserwartungen den Therapieerfolg beeinflussen. Patienten, die zu Behandlungsbeginn mehr Hoffnung auf Besserung in Bezug auf die

Behandlung haben, zeigen eine größere Verbesserung durch das Selbsthilfeprogramm. Durch die Studie konnte die Wichtigkeit von Behandlungserwartungen auch für internetbasierte Selbsthilfeprogramme verdeutlicht werden.

Da in Bezug auf negative Effekte von Psychotherapie noch wenig empirische Forschung besteht, sollte mithilfe von Studie 3 zunächst ein breiteres Verständnis für die Ursachen dieser negativen Effekte erlangt werden, bevor in Studie 4 der Einfluss von Behandlungserwartungen untersucht wurde. Dazu wurde in einer qualitativen Interviewstudie ein Kategoriensystem für Ursachen von negativen Effekten von Psychotherapie entwickelt. Mit *Gründe für Erfolglosigkeit oder Nebenwirkungen einer angemessenen Therapie*, *Probleme in der therapeutischen Beziehung*, *Gründe für Erfolglosigkeit oder Nebenwirkungen durch unprofessionelle Ausübung* und *Schädigung durch unethisches Verhalten des Therapeuten* konnten vier Hauptkategorien als Ursachen für negative Effekte von Psychotherapie identifiziert werden. In der nachgeschalteten Studie 4 konnte gezeigt werden, dass Behandlungserwartungen auch das Auftreten von negativen Effekten von Psychotherapie vorhersagen. Patienten, die zu Therapiebeginn weniger Hoffnung auf Besserung durch die Therapie hatten, berichteten mehr negative Effekte von Psychotherapie. Somit konnte durch unsere Studien 3 und 4 zum einen das Verständnis über negative Effekte von Psychotherapie erweitert werden, zum anderen konnten auch in diesem Bereich die Behandlungserwartungen als ein Einflussfaktor nachgewiesen werden.

5.1 Einschränkungen

Die Ergebnisse der Studien müssen vor dem Hintergrund einiger Einschränkungen betrachtet werden. In Studie 1 wäre es wünschenswert gewesen, noch eine unbehandelte Kontrollgruppe in das Design zu integrieren. Dies wird von anderen Forschern empfohlen (Colloca & Miller, 2011). Im aktuellen Fall hätte auch die Einnahme der Placebotablette bereits zur Ausbildung bestimmter Erwartungen führen können und somit einen Einfluss auf die berichteten Nebenwirkungen haben können. Da

es in der Kontrollgruppe jedoch keine Unterschiede in berichteten Nebenwirkungen zwischen Baseline, Akquisition und Evokation gibt, ist nicht davon auszugehen, dass ein solcher Effekt stattgefunden hat. Darüber hinaus sollte beachtet werden, dass die Studie an gesunden Probanden durchgeführt wurde und deshalb nicht auf eine klinische Stichprobe verallgemeinert werden kann. Zudem erfolgte die Tabletteneinnahme immer in Kombination mit einem neuartig schmeckenden Getränk, um die Einnahmesituation salienter zu gestalten, da so möglicherweise die konditionierte Reaktion gesteigert wird (Doering & Rief, 2012). In naturalistischen Settings ist die Tabletteneinnahme meist weniger salient, weshalb nicht geschlussfolgert werden kann, dass die Konditionierungseffekte hier gleich stark sind.

In internetbasierten Selbsthilfetrainings (Studie 2) liegen immer selektive Stichproben vor, da nur Patienten teilnehmen, die Zugang zu einem Computer und Internet haben und die motiviert genug sind an einem Selbsthilfeprogramm zu arbeiten. In Bezug auf die Behandlungserwartungen bedeutet dies möglicherweise auch, dass ohnehin eher Patienten mit hohen Behandlungserwartungen an dem Programm teilgenommen haben. Eine weitere Einschränkung der Studie ist die hohe Abbruchrate der Patienten zum Follow-up-Messzeitpunkt. Dies könnte bedeuten, dass nur Patienten, die mit der Behandlung zufrieden waren, den Follow-up-Fragebogen beantwortet haben. Aus diesem Grund müssen die Follow-up-Ergebnisse vorsichtig interpretiert werden.

Ein klarer Nachteil von Studie 3 und 4 ist, dass die negativen Effekte von Psychotherapie nur aus Patientenperspektive erhoben wurden. Optimal wäre es gewesen, die negativen Effekte auch aus Therapeutenperspektive zu erheben und zusätzlich von einem unbeteiligten Beobachter einschätzen zu lassen. Auf der anderen Seite kann man argumentieren, dass die Patienten diejenigen sind, die unter den negativen Effekten leiden und ihre Einschätzung, ob ein Effekt negativ ist, somit am relevantesten ist. In der 4. Studie war es uns aufgrund der Datenschutzpolitik der Kliniken leider

nicht möglich eine Follow-up-Erhebung durchzuführen. Da negative Effekte von Psychotherapie jedoch auch noch eine Weile nach Abschluss der Therapie auftreten können (Ladwig et al., 2014), wäre eine Follow-up-Messung sinnvoll gewesen. Darüber hinaus wäre eine Erfassung des Therapieerfolges in Form von Verbesserung der Hauptsymptomatik wünschenswert gewesen, da gezeigt werden konnte, dass dieser negativ mit negativen Effekten zusammenhängt (Moritz et al., 2015). Insbesondere im Hinblick auf den Einfluss der Behandlungserwartungen hätten so zusätzliche Analysen durchgeführt werden können, um ein tieferes Verständnis über den Zusammenhang zu erlangen, da die Behandlungserwartungen schließlich auch den Therapieerfolg beeinflussen.

5.2 Perspektiven für die Forschung und die klinische Praxis

Die Studien dieser Dissertation legen direkte nächste Schritte für zukünftige Forschung nahe. Um die Untersuchungen aus Studie 1 weiterzuführen und zu vertiefen, sollte das durchgeführte Experiment in einem nächsten Schritt an einer Stichprobe aus depressiven Patienten untersucht werden, um zu überprüfen, ob Vorerfahrungen mit einem Medikament in einer Patientenstichprobe einen ähnlichen Einfluss auf das Auftreten von Nebenwirkungen haben wie in einer gesunden Stichprobe. Als ein weiterer nächster Schritt wäre es dann sinnvoll, die Rolle von Erwartungen im Hinblick auf Nebenwirkungen von Medikamenten in naturalistischen Settings zu untersuchen. Als Vorstufe hierfür könnte überlegt werden, zunächst noch ein Experiment analog zu dem aus Studie 1 durchzuführen, bei dem jedoch der saliente Stimulus (neuartig schmeckendes Getränk) weggelassen wird. Weiterhin sollten die Untersuchungen auch auf weitere Substanzklassen, bei denen von hohen Nebenwirkungsraten ausgegangen werden kann, ausgeweitet werden.

Mit Studie 2 und 4 konnte das Wissen über Behandlungserwartungen im Kontext psychologischer Interventionen erweitert werden. In diesem Kontext könnte es für zukünftige Studien interessant sein zu untersuchen, wie Behandlungserwartungen in

Bezug auf psychologische Interventionen gebildet werden. Spielen auch hier vorherige Erfahrungen eine Rolle? Oder werden die Erwartungen über soziale Beobachtung oder die Aufnahme verbaler Informationen gebildet? Dies sind Fragen, die in weiteren Studien erforscht werden sollten. Darüber hinaus sollte der Einfluss von Behandlungserwartungen auf das Therapieergebnis bei internetbasierten Behandlungsprogrammen auch an weiteren Störungsbildern untersucht werden. In Bezug auf negative Effekte von Psychotherapie wäre es interessant zu untersuchen, wie der Zusammenhang zwischen Behandlungserwartungen, Therapieergebnis in Bezug auf die Hauptsymptomatik und negativen Effekten von Psychotherapie ist. Möglicherweise sagen Erwartungen die berichteten negativen Effekte von Psychotherapie vorher, da negative Effekte negativ mit Therapieerfolg korreliert sind und Therapieerfolg von Erwartungen vorhergesagt wird.

Die Ergebnisse der vorliegenden Dissertation haben auch Implikationen für die klinische Praxis. Da die durchgeführten Studien erneut die Wichtigkeit von Behandlungserwartungen im Kontext verschiedener Interventionen verdeutlichen konnten, wäre es wünschenswert, dass medizinisches und therapeutisches Personal im Hinblick darauf geschult wird. So könnten bereits vor Behandlungsbeginn durch gezielte Informationsvermittlungen die Behandlungserwartungen der Patienten gesteigert werden. Auch vorherige Erfahrungen mit einer Behandlung könnten so erfragt werden und im Falle negativer Vorerfahrungen könnte darauf reagiert werden, indem beispielsweise eine andere Behandlung angestrebt wird oder durch Informationsvermittlung versucht wird, die Erwartungen des Patienten in eine positivere Richtung zu lenken. Im Bereich von antihormoneller Therapie bei Brustkrebspatientinnen gibt es bereits eine erste Studie, die versucht durch Aufklärung der Patientinnen Nebenwirkungen durch die Therapie zu reduzieren (von Blanckenburg et al., 2015; von Blanckenburg, Schuricht, Albert, Rief, & Nestoriuc, 2013). Es wäre wünschenswert, dass dieses Vorgehen durch eine breite Schulung von Mitarbeitern im Gesundheitswesen in den medizinischen und therapeutischen Alltag integriert wird.

Mit der vorliegenden Arbeit ist es gelungen, einen breiten Überblick über die Rolle von Behandlungserwartungen in verschiedenen Interventionen und im Hinblick auf positive und negative Behandlungsergebnisse zu geben. Die bestehende Forschung konnte an entscheidenden Stellen ergänzt werden, um so den Weg für weitere Studien aber auch für die Implementierung einiger Prinzipien in die klinische Praxis zu ebnen.

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Appendix

A. Studien

A.1 Studie 1

Learning to experience side effects after antidepressant intake – Results from a randomized, controlled, double-blind study

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Conflicts of interest The authors Julia Rheker, Alexander Winkler, Bettina K. Doering, and Winfried 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. However, Bettina K. Doering has received honoraria from Biologische Heilmittel Heel for presentations on stress reactions. Winfried Rief has received honoraria from Biologische Heilmittel Heel, Berlin Chemie, and Bayer for presentations on placebo effects.

Abstract

Background. Side effects play a key role in patients' failure to take antidepressants. There is evidence that verbal suggestions and informed consent elicit expectations that can in turn trigger the occurrence of side effects. Prior experience or learning mechanisms are also assumed to contribute to the development of side effects, although their role has not been thoroughly investigated. In this study we examined whether an antidepressant's side effects can be learned via Pavlovian conditioning.

Methods. Participants (n = 39) were randomly allocated to one of two groups and were exposed to a classical conditioning procedure. During acquisition, 19 participants received amitriptyline and 20 participants received a placebo pill. Pills were taken for four nights together with a novel-tasting drink. After a washout-phase, both groups received a placebo pill together with the novel-tasting drink (evocation). Side effects were assessed via the Generic Assessment of Side Effects Scale prior to acquisition (baseline), after acquisition, and after evocation. A score of antidepressant-specific side effects was calculated.

Results. Participants taking amitriptyline reported significantly more antidepressant-specific side effects after acquisition compared to both baseline and the placebo group. After evocation, participants who underwent the conditioning procedure with amitriptyline reported significantly more antidepressant-specific side effects than those who never received amitriptyline, even though both groups received a placebo.

Conclusions. Our results indicate that antidepressant side effects can be learned using a conditioning paradigm, and evoked via a placebo pill when applied with the same contextual factors as the verum.

Keywords: side effects, nocebo, antidepressants, learning

1. Introduction

The prescribing of antidepressants has risen over recent years, with up to 13.4% of individuals in Western countries having been prescribed antidepressant medication at least once per year (Sihvo et al. 2010; Lockhart and Guthrie 2011; Mojtabai and Olfson 2014; Abbing-Karahagopian et al. 2014). Although antidepressants are effective in treating major depression (Cleare et al. 2015), patients often discontinue drug intake (Sawada et al. 2009; Bocquier et al. 2014). Rates of reported non-adherence vary, but some studies report rates of discontinuing antidepressant medication of over 50% within the first two to four months (Serna et al. 2010), while others report even higher discontinuation rates (Bocquier et al. 2014). These rates are alarming considering that guidelines suggest taking antidepressant medication for at least 6 to 9 months to prevent relapse after the remission of a depressive episode (Cleare et al. 2015). Several factors contributing to patients' non-adherence have been identified (Serna et al. 2010; De las Cuevas et al. 2014; Bocquier et al. 2014), but one particular factor emerges consistently as a reason for discontinuing antidepressants, namely side effects (e.g., Serna et al. 2010; Hung et al. 2011; Murata and Kanbayashi 2012; De las Cuevas et al. 2014). Common side effects of antidepressants (i.e. pharmacological reactions due to drug intake that differ from those intended) are for instance daytime sleepiness, dry mouth, loss of interest in sexual activity, and weight gain (Ashton et al. 2005).

Some of the adverse events occurring after medication intake can be attributed to the drug's specific pharmacological action, and many such events are considered to be dose-dependent, whereas others, not attributable to the drug's pharmacological action, often appear to be dosage-independent (Shedden Mora et al. 2011). The latter events can be studied in placebo groups in drug trials: All side effects occurring after the intake of an inert substance are not specific or attributable to the drugs' pharmacokinetics (Schedlowski et al. 2015). The occurrence of side effects after placebo intake is called the nocebo effect. Originally, it was assumed that some nocebo side effects occur due to the misattribution of pre-existing symptoms (Barsky et al. 2002). More recent studies have additionally shown that the adverse effects occurring in placebo groups in drug trials match the side effects reported in the active drug arms of these trials (e.g., Rief et al. 2009; Amanzio et al. 2009; Mitsikostas 2012).

One explanation for the nocebo phenomenon is patients' expectations about possible side effects in general (Nestoriuc et al. 2010), which might be triggered by the information provided in the informed consent or by verbal suggestion (Mondaini et al. 2007; Cohen 2014). Another factor potentially contributing to the occurrence of side effects is prior experience or learning (Amanzio 2015). One such example is cancer patients experiencing nausea as a side effect after undergoing chemotherapy. It is assumed that initially, neutral stimuli such as the room in which the therapy is administered are associated with the occurrence of nausea: therefore, just entering the room can cause anticipatory nausea after a while (Matteson et al. 2002). Such conditioning effects can be generated if an originally neutral stimulus (NS; e.g., the room) is combined with an active stimulus (unconditioned stimulus = UCS; e.g., chemotherapy) that leads to certain reactions (e.g., nausea). After several pairings of NS and UCS (acquisition phase), the NS becomes a conditioned stimulus (CS). This means that the CS alone can evoke the reaction that was originally generated by the UCS (evocation; Pavlov 2010). Although some authors differentiate between expectations and conditioning as different mechanisms involved in placebo and nocebo responses (Enck et al. 2013), it is not always possible to clearly distinguish them since learning also leads to certain expectations (Stewart-Williams and Podd 2004). Therefore, in this article, we do not differentiate between expectation and conditioning per se but rather between "expectation through verbal suggestion" and "learning/conditioning".

Learning effects have been experimentally investigated, showing, for example, that with motion sickness, a nocebo response can be learned (Klosterhalfen et al. 2009). Colloca et al. (2008) found in a conditioning paradigm that a light paired with a noxious stimulus can induce a hyperalgesic nocebo effect in the evocation trial. In a subsequent study using a similar paradigm, they showed that even one acquisition trial suffices to induce nocebo effects, although effects are more stable after additional trials (Colloca et al. 2010). Conditioned nocebo effects can also be evoked by non-conscious stimuli (Jensen et al. 2012).

When it comes to pharmacological responses, the role of conditioning has been demonstrated in conjunction with immune reactions (Albring et al. 2012). However, to the best of our knowledge, there has been no evidence forthcoming that reveals whether Pavlovian conditioning contributes to the development and maintenance of antidepressant side effects.

We hypothesized that participants taking amitriptyline would report more antidepressant-specific side effects in all after four nights of medication intake (acquisition phase, i.e., pill intake combined with a novel-tasting drink as NS) and attribute more of these side effects to the medication intake than would participants taking a placebo. Furthermore, we hypothesized that after having undergone the aforementioned acquisition and a subsequent wash-out phase, receiving a placebo pill together with the novel-tasting drink (evocation) would lead to more reported antidepressant-specific side effects in total and more medication-attributed antidepressant-specific side effects in the group that had previously taken amitriptyline than in the placebo group.

2. Methods

2.1. Participants and ethics

This study was conducted in the Division of Clinical Psychology at the Philipps-University of Marburg in 2014. Participants aged between 18 and 69 years who were willing to refrain from alcohol consumption and driving during the study period were recruited via an advertisement at the University. To ascertain that only physically and mentally healthy participants were included, all subjects underwent a medical and psychological examination (by a study physician and a psychologist, both trained in Good Clinical Practice). These included interviews about medical history and mental health (according to the International Diagnosis Checklists (Hiller et al. 2004)), an electrocardiogram, blood tests, and a urine pregnancy test (only in females). If the examinations yielded evidence of contraindications to the study medication as mentioned in the information sheet for health professionals, those participants were excluded.

Prior to the beginning of the study, participants were informed about the study design and treatment by the study physician. Written informed consent was obtained from all individual participants included in the study. The experiment was conducted according to the Declaration of Helsinki. Since the current study was only an exploratory sub-investigation in addition to the main study (for detailed results see Winkler et al. 2016), only the main study was registered at www.clinicaltrials.gov (NCT02127736). Nevertheless, the outcomes used in this study were determined as secondary outcome measures in the study protocol, which was approved by the ethics committee of the medical

chamber of Hessen (Landesärztekammer Hessen; FF51/2013). Participants were paid for study participation.

2.2. Experimental design

After the medical and psychological examination, equal numbers of participants were randomized into the placebo and antidepressant groups, no stratification was conducted. Randomization was done by an independent researcher. Through randomization each individual got a number, which was assigned to a medication container which held either placebo or antidepressant pills. Both experimenters and participants were blinded to group allocation. The experimental group received amitriptyline; the control group received identical-looking placebo pills. At the baseline assessment, all subjects filled in the Generic Assessment of Side Effects Scale (GASE; Rief et al. 2010). Afterwards, participants in the experimental group underwent a classical conditioning paradigm (see Figure 1). During the acquisition phase (nights one to four), participants received 50mg of amitriptyline (US) together with 100ml of a novel-tasting drink that consisted of lychee juice with woodruff syrup and blue food coloring. The drink was the neutral stimulus (NS), which was supposed to become the conditioned stimulus (CS). The drinks' ingredients were chosen in order to increase the novelty, saliency and distinctiveness of the CS, since it has been argued that this might increase the conditioned response (Doering and Rief 2012). Amitriptyline-neuraxpharm 50mg was used and encapsulated for study purposes by licensed pharmacologists. To make pill intake more salient a novel tasting drink was used. Participants were instructed to take the medication and the novel-tasting drink immediately before going to bed on four subsequent nights. Once the acquisition phase was over, side effects during acquisition were assessed. The acquisition was followed by a three-day washout phase (nights five to seven). On night eight, the evocation night, all participants received a placebo pill together with the novel-tasting drink (CS). The next day, side effects after evocation were assessed.

The placebo control group underwent the same procedure as the experimental group, but received placebo pills instead of amitriptyline during the acquisition phase.

- Insert Figure 1 about here -

Fig 1 Experimental design

2.3. Measures

Side effects were assessed with the Generic Assessment of Side Effects Scale (GASE; Rief et al. 2010). The GASE contains a list of 36 symptoms, and covers the most frequently reported side effects in clinical trials using different drugs according to FDA. The patient gives a rating for the presence and severity of each of these symptoms on a 4-point-Likert scale ranging from "not present" (0) to "severe" (3). In addition, the patient indicates for each symptom whether he or she thinks it is caused by the intake of the drug (yes/no). A total score can be calculated as a sum of all item answers (general symptom load) as well as a total score of only medication-attributed symptoms. The GASE reveals good internal consistency with Cronbach's $\alpha = 0.89$ and has been validated in a large sample with more than 2,500 participants (Rief et al. 2010).

Primary Outcome Measure. For the purpose of our study, an Antidepressant Composite Score (GASE-AD) was calculated to assess side effects specific for the study's antidepressant. To assess the most frequently reported side effects, we chose items that at least 50% of the experimental group had experienced after the acquisition phase. This criterion left us with four items: (1) dry mouth, (2) dizziness, (3) cardiovascular problems, (4) fatigue, loss of energy. These symptoms are also listed in the Physician's Desk Reference (Barnhart 1988) and in the Compendium of Psychiatric Pharmacotherapy (Benkert and Hippius 2014) as common symptoms of amitriptyline. In addition, these four symptoms are listed among twelve very common symptoms of amitriptyline on www.pharmawiki.ch (2015). We then calculated the score of all reported antidepressant specific side effects (GASE-AD) and that of all medication-attributed antidepressant specific side effects (GASE-AD-MA). Detailed analyses of potentially positive placebo effects are reported elsewhere (Winkler et al. 2016).

Further analyses. In addition to studying antidepressant-specific side effects, we analyzed more generic side effects or symptoms also, since symptoms not specific to the drug under investigation can also occur after taking a placebo pill (Barsky et al. 2002). For this purpose, the four antidepressant-specific items were excluded from calculating the scales for all reported generic, i.e. not antidepressant-specific side effects (GASE-generic) and for all medication-attributed generic side

effects (GASE-generic-MA). To give a complete overview of reported side effects, we also analyzed the complete GASE scale (GASE-total) and calculated a score for all common side effects of amitriptyline (GASE-AMI) independent of how often they were named in the experimental group after acquisition. This score contains the items that are mentioned as the most frequently reported side effects both in the Compendium of Psychiatric Pharmacotherapy (Benkert and Hippius 2014) and on www.pharmawiki.ch. The items in the score are: (1) dry mouth, (2) dizziness, (3) cardiovascular problems, (4) fatigue, loss of energy, (5) palpitations, irregular heartbeat, (6) constipation, (7) abnormal sweating, and (8) tremor. Weight gain was not included in the score since participants only took amitriptyline for four days. In addition, accommodation problems were also not included in the score because it was not assessed in the GASE. For the GASE-total and the GASE-AMI medication attributed scores were calculated as well (GASE-total-MA and GASE-AMI-MA).

To assess whether participants were unblinded by amitriptyline's experienced side effect profile, we asked the participants after the acquisition phase to guess which experimental group (amitriptyline vs. placebo) they belonged to. After study completion and unblinding, this rating (perceived group allocation) was correlated with current group allocation.

To analyze any clinical correlates with the nocebo response, we applied the subscales of the Symptom Checklist-90-Revised (SCL-90-R; Derogatis 1994), and the Beck Depression Inventory (BDI; Beck et al. 1961), which were assessed at baseline, and correlated those with the GASE-AD and GASE-AD-MA.

2.4. Statistical analyses

We calculated the sample size with G*Power (Faul et al. 2007). The initial sample size for the study was calculated for the primary outcome in the main study (Winkler et al. 2016), hence only 40 participants were recruited. However, for the current investigation the sample size was calculated post-hoc and revealed that in order to detect a large time*group interaction effect with a power of 80% and an α-level of 0.05, the estimated total sample size was $n = 42$.

Statistical analyses were performed with IBM SPSS Statistics 21.0. Baseline characteristics were analyzed using t-tests and χ^2-tests. Missing values in the GASE were replaced by multiple imputation.

To test for differences in total side effect reporting and medication-attributed side effect reporting between and within groups, multivariate analyses of variance (MANOVA) for repeated measures with the factors time (baseline, acquisition, evocation) and group (amitriptyline or placebo) were applied. Significant effects in the MANOVA were followed-up by pairwise comparisons. The pairwise comparisons were adjusted according to the Bonferroni procedure, i.e., the within-group tests were adjusted for three comparisons each. The correlation between current group allocation and perceived group allocation was calculated via the phi coefficient. Correlations between the SCL-90-R subscales and the BDI and the GASE scales were calculated using the Pearson correlation coefficient.

3. Results

Forty participants were recruited and randomized equally to the two groups. In the experimental group, one participant discontinued drug intake due to side effects and was therefore excluded from study participation. Nineteen subjects in the amitriptyline group and 20 subjects in the placebo control group were thus included in our analyses (see Figure 2). There were no significant differences in age, sex, or weight between participants in the two groups at baseline (see Table 1).

- Insert Figure 2 about here -

Fig 2 Flowchart

Table 1 Sample Characteristics

Characteristics	Amitriptyline (n=19)	Placebo (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)	χ^2 (1) = 0.03, p = .556
Weight in kg, *M (SD)*	67.5 (11.3)	63.9 (9.0)	t (36[a]) = -1.09, p = .285

Note: [a] one participant in the placebo group did not answer this question

3.1. Primary outcome – Antidepressant-specific side effects

GASE-AD (antidepressant-specific side effects). Overall multivariate analyses offered the basis for subsequent pairwise comparisons of single conditions (group effect F (2, 36) = 13.26; $p \leq .001$, time effect F (4, 34) = 10.33; $p \leq .001$, group*time interaction effect F (4, 34) = 8.17; $p \leq .001$; univariate analyses: group effect F (1, 37) = 11.27; p = .002, time effect F (1, 37) = 14.57; $p \leq .001$, group*time

interaction effect F (1, 37) = 14.37; $p \leq .001$). We observed that the two groups differed significantly in reported antidepressant-specific side effects after the acquisition phase ($p \leq .001$; effect size Hedge's g = 1.56; 95% Confidence Interval (CI): 0.84 – 2.28) and after the evocation night (p = .045; g = 0.66; CI: 0.01 – 1.30): the amitriptyline group reported significantly more side effects (see Table 2 and Figure 3a). Furthermore, the amitriptyline group displayed significant differences between baseline and acquisition ($p \leq .001$), between baseline and evocation (p = .007), and between acquisition and evocation ($p \leq .001$). After the acquisition phase, subjects in the experimental group reported significantly more side effects compared with baseline and evocation. After the evocation night, participants also reported significantly more side effects compared with baseline.

GASE-AD-MA (medication-attributed antidepressant-specific side effects). We found that the amitriptyline group's medication-attributed, antidepressant-specific side effects score was significantly higher after the acquisition phase ($p \leq .001$; g = 1.75; CI: 1.02 – 2.49) and after the evocation night (p = .008; g = 0.88; CI: 0.22 – 1.54) than the placebo group's (see Table 2 and Figure 3b). We also noted significant within-group-differences between both baseline and acquisition ($p \leq .001$), and between baseline and evocation (p = .001) on the GASE-AD-MA in the amitriptyline group. Thus, more antidepressant-specific side effects were attributed to the medication after the acquisition phase (i.e. intake of amitriptyline for four nights) than at baseline. More importantly, however, more antidepressant-specific side effects were also reported as medication-attributed after evocation night (i.e. after placebo intake) than at baseline. Furthermore, the amitriptyline group also reported significantly more medication-attributed symptoms after the acquisition phase than after the evocation night (p = .006; univariate analyses: group effect F (1, 37) = 27.21; $p \leq .001$, time effect F (1, 37) = 17.31; $p \leq .001$, group*time interaction effect F (1, 37) = 14.12; $p \leq .001$).

Table 2 Means, standard deviations, and F-statistics for the univariate analyses for the different side effects scores

	Amitriptyline *M (SD)*	Placebo *M (SD)*	Time effect	Group effect	Interaction
Primary Outcome					
GASE-AD			F (1, 37) = 14.57**	F (1, 37) = 11.27*	F (1, 37) = 14.37**
Baseline	0.89 (0.88)	1.10 (1.37)			
Acquisition	4.37 (2.45)	1.10 (1.59)			
Evocation	2.35 (2.49)	0.98 (1.51)			
GASE-AD-MA			F (1, 37) = 17.31**	F (1, 37) = 27.21**	F (1, 37) = 14.12**
Baseline	0 (0)	0 (0)			
Acquisition	3.48 (2.59)	0.18 (0.51)			
Evocation	1.74 (2.58)	0.10 (0.45)			
Further analyses					
GASE-generic			F (1, 37) = 0.84	F (1, 37) = 0.23	F (1, 37) = 2.05
Baseline	4.32 (3.68)	3.75 (3.68)			
Acquisition	5.63 (4.78)	3.85 (3.69)			
Evocation	3.68 (3.43)	4.42 (5.49)			
GASE-generic-MA			F (0.60, 22.20)[a] = 5.43*	F (0.60, 22.20)[a] = 3.88	F (0.60, 22.20)[a] = 2.87
Baseline	0 (0)	0 (0)			
Acquisition	1.87 (3.40)	0.37 (1.09)			
Evocation	0.48 (0.91)	0.21 (0.90)			
GASE-total			F (0.85, 31.48)[a] = 5.61*	F (0.85, 31.48)[a] = 2.13	F (0.85, 31.48)[a] = 6.11*
Baseline	5.21 (3.55)	4.85 (4.80)			
Acquisition	10.00 (5.24)	4.95 (4.95)			
Evocation	6.03 (4.58)	5.40 (6.77)			
GASE-total-MA			F (0.76, 22.28)[a] = 14.53**	F (0.76, 22.28)[a] = 23.45**	F (0.76, 22.28)[a] = 10.04*
Baseline	0 (0)	0 (0)			
Acquisition	5.36 (4.69)	0.55 (1.57)			
Evocation	2.22 (3.17)	0.31 (1.34)			
GASE-AMI			F (1, 37) = 14.52**	F (1, 37) = 9.13*	F (1, 37) = 15.08**
Baseline	1.05 (1.13)	1.40 (1.89)			
Acquisition	5.33 (2.91)	1.35 (2.11)			
Evocation	2.87 (2.84)	1.28 (2.41)			
GASE-AMI-MA			F (1, 37) = 17.01**	F (1, 37) = 31.54**	F (1, 37) = 14.98**
Baseline	0 (0)	0 (0)			
Acquisition	4.06 (2.86)	0.18 (0.51)			
Evocation	1.89 (2.88)	0.10 (0.45)			

Note: GASE-AD = Antidepressant Composite Score of the Generic Assessment of Side Effects Scale; GASE-AD-MA = medication attributed symptoms of the Antidepressant Composite Score of the Generic Assessment of Side Effects Scale; GASE-generic = Generic symptoms on the Generic Assessment of Side Effects Scale; GASE-generic-MA = medication attributed generic symptoms on the Generic Assessment of Side Effects Scale; GASE-total = all reported side effects as assessed with the Generic Assessment of Side Effects Scale; GASE-total-MA = all medication attributed side effects as assessed with the Generic Assessment of Side Effects Scale; GASE-AMI = score of all common side effects of amitriptyline; GASE-AMI-MA = score of all medication attributed common side effects of amitriptyline; * $p \leq .05$; ** $p \leq .001$; [a] = degrees of freedom have been corrected according to Greenhous-Geisser

- Insert Figure 3 about here -

Fig 3 Antidepressant-specific side effects for both groups and all time points
Note: GASE-AD = Antidepressant Composite Score of the Generic Assessment of Side Effects Scale; GASE-AD-MA = medication attributed symptoms of the Antidepressant Composite Score of the Generic Assessment of Side Effects Scale

3.2. Further analyses

GASE-generic (generic side effects): Our results reveal that only in the amitriptyline group there was a significant difference between baseline and acquisition phase in medication-attributed generic side effects (GASE-generic-MA; $p = .007$). Participants attributed more generic symptoms to the medication after the acquisition phase than at baseline. We observed no differences between the groups in either the GASE-generic or GASE-generic-MA (multivariate analyses: group effect: $F(2, 36) = 1.89$; $p = .166$, time effect: $F(4, 34) = 2.83$; $p = .040$, group*time interaction effect: $F(4, 34) = 2.19$; $p = .091$; univariate analyses regarding GASE-generic-MA: time effect $F(0.60, 22.20) = 5.43$; $p = .027$).

GASE-total (all side effects). The experimental group reported significantly more total side effects (GASE-total) at acquisition than the control group ($p = .003$) and it reported significantly more medication attributed total side effects (GASE-total-MA) at acquisition ($p \leq .001$) and at evocation ($p = .018$). Only for the experimental group significant within-group differences between the assessment points could be observed for the GASE total score between baseline and acquisition ($p \leq .001$) and between acquisition and evocation ($p = .008$). For the GASE-total-MA significant differences between all assessment points could be observed in the experimental group (multivariate analyses: group effect $F(2, 36) = 11.46$; $p \leq .001$, time effect $F(4, 34) = 8.80$; $p \leq .001$, group*time interaction effect $F(4, 34) = 6.75$; $p \leq .001$; for detailed results of the univariate analyses see Table 2).

GASE-AMI (common side effects of amitriptyline). Pairwise comparisons showed that there were significant group differences at acquisition in the GASE-AMI score ($p \leq .001$) with the experimental group reporting more side effects. In the medication-attributed score for common side effects of amitriptyline (GASE-AMI-MA) groups differed significantly at acquisition ($p \leq .001$) and at evocation ($p = .009$) in the direction that the experimental group reported more side effects. For the experimental group within-group-differences were significant for comparisons between all time points on the

GASE-AMI and on the GASE-AMI-MA (multivariate analyses: group effect $F(2, 36) = 15.35$; $p \leq .001$, time effect $F(4, 34) = 11.61$; $p \leq .001$, group*time interaction effect $F(4, 34) = 9.89$; $p \leq .001$; for detailed results of the univariate analyses see Table 2).

Perceived group allocation. Group allocation as rated subjectively by the participants after the acquisition phase (perceived group allocation) correlated significantly with actual group allocation ($\varphi = .641$), meaning that 82% of participants guessed their group allocation correctly, indicating the participants' at least partial unblinding to group allocation.

Nocebo response correlates. We detected no significant correlations among either the SCL-90-R subscales or BDI and the GASE-AD and GASE-AD-MA at any timepoint (baseline, acquisition, or evocation) in the amitriptyline group, indicating the nocebo response's independence of these clinical features.

4. Discussion

The aim of our study was to investigate whether antidepressant-specific side effects are not only caused by the drug's pharmacological actions but also learned through classical conditioning. We found that antidepressant-specific side effects can be evoked by an identical-looking placebo pill in participants who had previously taken an antidepressant that was accompanied by the same stimulus (novel-tasting drink) as the intake of placebo. In addition, participants who had previously been taking the antidepressant rated more of the side effects after taking the placebo pill as being medication-induced than participants who had been taking the placebo all the time. In contrast to the antidepressants' specific side effects, the generic side effects score did not change significantly between the assessment points, although participants taking amitriptyline attributed more of these generic side effects to medication intake after acquisition.

These findings suggest that learning plays a role in the experiencing and reporting of side effects from antidepressants. This result is highly relevant, since patients suffering from depression often experience several depressive episodes in their lives and usually undergo repeated pharmacological treatment (Solomon and Keller 2000). There is evidence that patients who have been prescribed antidepressant medication once are more likely to be prescribed antidepressants again (Sirey and

Meyers 2014). Our results suggest that if a participant has had negative experiences with a certain drug before, learning processes may contribute to the re-occurrence of these side effects. This in turn may lead to non-adherence or drug discontinuation (e.g., Serna et al. 2010; Hung et al. 2011; Murata and Kanbayashi 2012; De las Cuevas et al. 2014) and hence to a worse outcome or higher risk of relapses (Åkerblad et al. 2006). Given that side effects seem to depend on prior experience, it would seem advisable to systematically assess a patient's prior experience with specific drugs before issuing a prescription, and in case of negative experiences to try another drug (Doering and Rief 2013).

Our finding that certain side effects can be learned is in line with research showing that learning plays an important role in nocebo effects (e.g., Colloca et al. 2008; Klosterhalfen et al. 2009). Furthermore, it also falls in line with studies demonstrating that pharmacological responses can be conditioned (Goebel et al. 2008; Attwood et al. 2010; Albring et al. 2012). There have been proposals and even tests involving conditioning procedures to reduce drug doses in pharmacotherapy, a mechanism called placebo-controlled dose reduction (Ader et al. 2010; for a review see Doering and Rief 2012). The maintenance of a drug's therapeutic effect while possibly reducing side effects and hence enhancing compliance has been postulated as one advantage of placebo-controlled dose reduction (Doering and Rief 2012). However, both the placebo effect of drug intake can obviously be learned, as can the nocebo effect, a factor that should be considered when planning placebo-controlled dose reduction.

Participants taking amitriptyline attributed more generic symptoms to medication intake, although their generic-symptoms score after acquisition was not significantly higher than their own baseline and the placebo group's scores, revealing that part of the side effects patients report may be due to the misattribution of pre-existing symptoms. By thoroughly assessing symptoms and side-effects including baseline evaluations (Rief et al. 2006), we have succeeded in demonstrating this "misassignment" of symptom attribution. This is an already-described phenomenon (Barsky et al. 2002). The effect in our study was admittedly rather small and needs to be replicated. However, it is an extremely relevant phenomenon in pharmacotherapy since the attribution of side effects to the medication is an important factor behind the discontinuation of medication intake.

Some shortcomings of the present study should be mentioned. First, we only assessed subjective data as outcome measures. Participants may have reported more symptoms in general because they were taking a drug, even though they did not attribute them to that drug. To account for this bias, we differentiated between reported symptoms in general and medication-attributed symptoms. In addition, the structured assessment of side effects (rather than an unstructured evaluation) may trigger more reported side effects (Rief et al. 2006). Secondly, the correlation between perceived group allocation and actual group allocation indicates that at least some participants were unblinded to group allocation, a problem reported and discussed in previous antidepressant trials in general (Jeffrey et al. 1986; Margraf et al. 1991). In terms of our study, this might imply that the unblinding shaped the participants' expectations regarding the pill in the evocation night, with the amitriptyline group expecting more side effects. Thirdly, the generalizability of our results to a clinical setting is limited since we only examined healthy young individuals and always paired the drug intake with a salient new stimulus. Hence, we cannot conclude whether a paradigm in which only the pill's appearance (without a salient new stimulus) in the typical treatment context serves as the conditioned stimulus (the case in natural clinical settings) would evoke the same amount of side effects. A fourth limitation is that since this study was just a pilot trial, we did not incorporate an untreated group in the study design, something other researchers suggest (Colloca and Miller 2011). Finally, it is a shortcoming that it would have been advantageous to include an assessment of side effects after the washout phase in order to control for any residual symptoms from the acquisition phase. One could argue that the side effects occurring in the evocation night were only due to a residual concentration of amitriptyline in the blood. However, there is solid evidence that the plasma half-life of tricylic antidepressants ranges from 10 to 28 hours (Rudorfer and Potter 1999). Our washout phase entailed three nights without medication intake, which is 86 hours between the last intake of amitriptyline and intake of placebo and should rule out the argument that a residual concentration of amitriptyline might have accounted for the difference in the evocation night. In addition, our participants received only low doses of amitriptyline (50mg). Nevertheless, one could also argue that the antidepressant-specific side effects reported in the evocation night were due to discontinuation effects of amitriptyline, which might include gastrointestinal symptoms, affective symptoms, general somatic symptoms, and sleep

disturbance (Haddad and Anderson 2007). However, the longer the treatment lasts and the higher the dosage of antidepressant, the more likely discontinuation symptoms occur (Kramer et al. 1961; Perahia et al. 2005). Both of these circumstances do not apply to our study, meaning that the explanation that differences between the amitriptyline and placebo group at the evocation night were only due to discontinuation effects is not likely.

Despite these limitations, our study encourages future research to examine Pavlovian conditioning in conjunction with side effects. To learn more about these mechanisms, future studies should vary the number of learning trials and of the intervals between acquisition and evocation. It would be critical to determine if and when conditioned effects extinguish when the interval between acquisition and evocation is long enough. In addition, we only examined the effect associated with one drug, thus the learning of side effects should also be addressed in conjunction with other drugs. To draw conclusions for pharmacotherapy in clinical settings, patients rather than healthy individuals need to be examined. Understanding the mechanisms that lead to the learning of side effects may help to prevent the side effects triggered by prior experience. Several proposals about how to reduce side effects have been made (Colloca and Miller 2011; Bingel 2014). Such interventions focus mainly on the expectations of side effects induced by verbal suggestion or other information, and how to modify them to minimize side effects (von Blanckenburg et al. 2013). As our findings suggest that prior negative experience with a drug can also lead to side effects and hence non-adherence, it is important to develop additional strategies to prevent these learned side effects.

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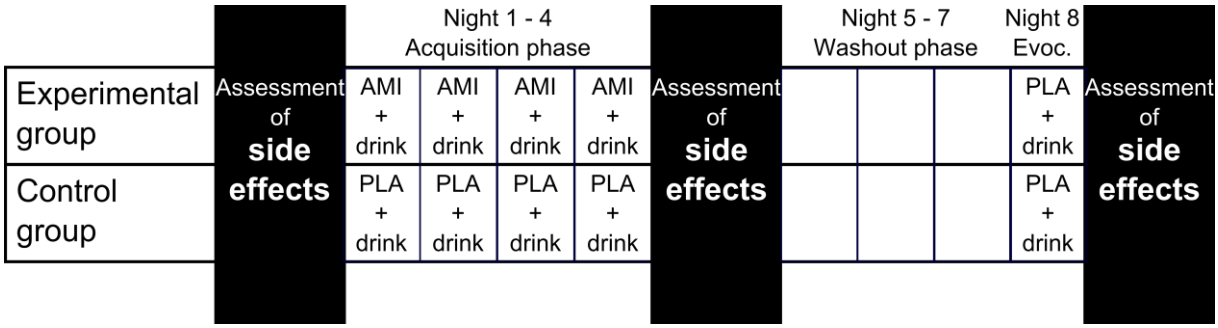

Fig 2 Experimental design

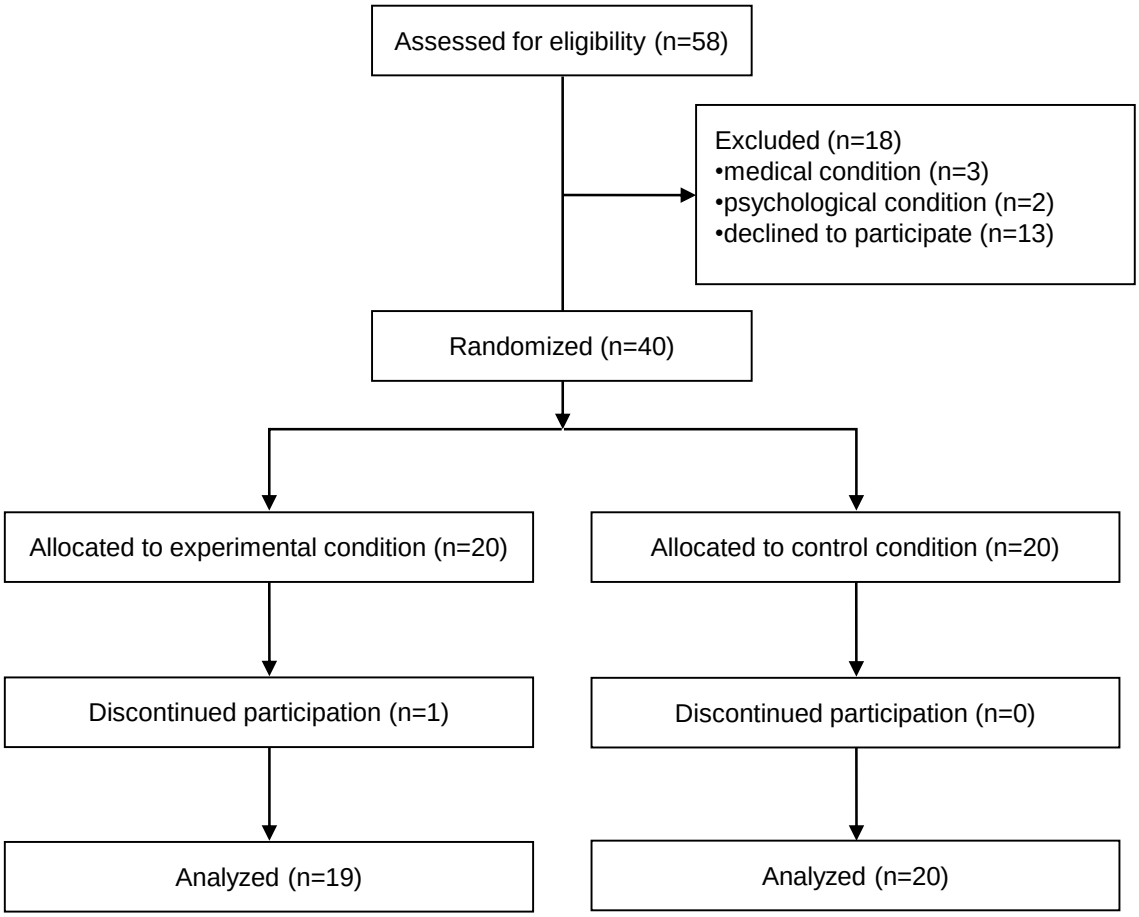

Fig 2 Flowchart

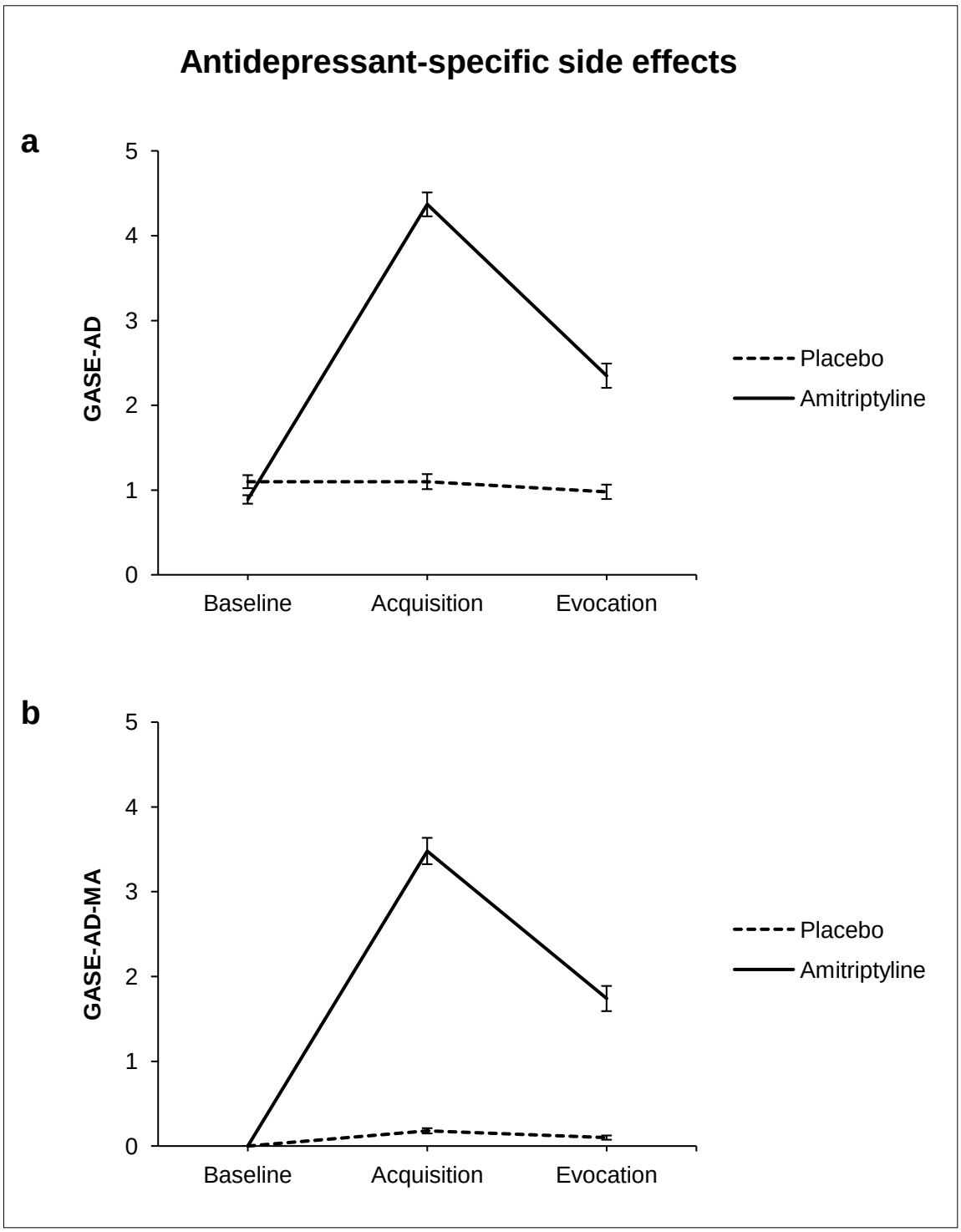

Fig 3 Antidepressant-specific side effects for both groups and all time points

Note: GASE-AD = Antidepressant Composite Score of the Generic Assessment of Side Effects Scale; GASE-AD-MA = medication attributed symptoms of the Antidepressant Composite Score of the Generic Assessment of Side Effects Scale

A.2 Studie 2

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The role of "on demand" therapist guidance vs. no support in the treatment of tinnitus via the internet: A randomized controlled trial

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ABSTRACT

Objective: Internet-based cognitive behavioral self-help treatments (iCBT) have been shown to successfully reduce the distress associated with tinnitus. Despite this success, little is known about the mechanisms that make iCBT for tinnitus sufferers work. Availability of minimal therapeutic support is assumed to positively influence treatment outcome in iCBT, but the lower limit of required support is not known. In face-to-face therapy, patients' positive outcome expectations have demonstrated an advantageous effect on outcome. The first aim of our study was thus to investigate the role of 'on demand' therapeutic guidance vs. no therapeutic support on treatment outcome in an iCBT for tinnitus sufferers. Our second aim was to investigate whether positive outcome expectations can predict treatment outcome.
Methods: A total of 112 tinnitus patients were randomly assigned to one of two groups (support-on-demand or non-support). Both groups received an established iCBT treatment for tinnitus. While participants in the support group ($n = 56$) could ask a therapist for additional support, those in the other ($n = 56$) received no therapeutic guidance. Tinnitus distress was assessed pre- and post-treatment via the Tinnitus Handicap Inventory (THI) and the Mini-Tinnitus Questionnaire (Mini-TQ). Pre-treatment outcome expectations were assessed using the Patient Questionnaire on Therapy Expectation and Evaluation (PATHEV).
Results: We observed significantly less tinnitus distress in the THI (support: $t(55) = 7.51$, $p \leq .001$; non-support: $t(55) = 7.68$, $p \leq .001$) and Mini-TQ (support: $t(55) = 8.24$, $p \leq .001$; non-support: $t(55) = 8.46$, $p \leq .001$) in both groups from pre- to post-treatment, but no significant differences between the groups or interactions. The PATHEV subscale "Hope of Improvement" significantly predicted treatment outcome as measured by the THI ($\beta = 0.28$, $p = .027$).
Conclusions: The iCBT self-help program is a good treatment option for tinnitus sufferers whether or not support-on-demand is provided. Furthermore, our results show the importance of outcome expectations to the efficacy of iCBT in tinnitus patients. Future research should focus on discovering further predictors of treatment outcome.

1. Introduction

Tinnitus is referred to as the perception of sound (e.g., ringing, hissing) without any external sound stimulation (Lockwood et al., 2002). Studies indicate that between 2–9% of the population suffer from distressing tinnitus (Hasson et al., 2010; Kuttila et al., 2005; Pilgramm et al., 1999; Shargorodsky et al., 2010). Chronic tinnitus can cause several associated problems, for instance, sleeping problems, concentration difficulties, or depressive symptoms (Andersson et al., 2004; Henry et al., 2005), and thus severely affect the sufferers' quality of life and lifestyle (Kennedy et al., 2004). There is no evidence of medical treatments that cure chronic tinnitus (Baguley et al., 2013). The distress associated with tinnitus can be effectively targeted by cognitive behavioral treatment (CBT; Hesser et al., 2011; Martinez-Devesa et al., 2009; Weise et al., 2008). Unfortunately, there is a lack of clinicians offering tinnitus-specific treatment (Gander et al., 2011). Current research is therefore increasingly focused on CBT-self-help as a treatment option for tinnitus patients (Nyenhuis et al., 2013a,b), in particular on self-help programs delivered via the internet (iCBT; Andersson, 2014). Results have been promising for the reduction in tinnitus distress and associated problems (e.g., Hesser et al., 2012; Jasper et al., 2014).

For tinnitus sufferers in particular, iCBT has advantages beyond giving more patients access to treatment. Tinnitus patients often have a predominantly somatic perception of their tinnitus, indicating that traditional psychotherapy can possess lower face validity (Weise et al.,

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2008; Wickramasekera, 1989). Some patients fear being stigmatized by psychotherapy and thus refrain from seeking mental health treatment (Kendra et al., 2014). iCBT might help to overcome these problems as it is more anonymous, reduces the stigma of going to a psychotherapist, and it appears at first to be more technical and less "psychological" (Cuijpers et al., 2008; Gega et al., 2013).

While iCBT's efficacy has been proven for several disorders in several randomized controlled trials (RCTs), we do not know which factors make it work. In traditional face-to-face therapy, common factors such as the therapeutic relationship, therapist confidence, and patients' outcome expectations are assumed to have a positive impact on therapy outcome (Lambert and Ogles, 2004; Lambert, 2005). Studies on internet-delivered treatments have examined some of these, especially the role of therapeutic support and expectations (Andersson et al., 2013; Boettcher et al., 2013; Carlbring and Andersson, 2006; Palmqvist et al., 2007; Spek et al., 2007). Whereas findings regarding the role of expectations in iCBT are mixed (e.g., Boettcher et al., 2013; Kaldo et al., 2008), results show that the presence of at least minimal therapeutic support is supposed to play an important role in the efficacy of iCBT (e.g., Baumeister et al., 2014).

Several RCTs have addressed iCBT with therapeutic support in tinnitus sufferers and reported medium-to-large pre–post effect sizes (Cohen's d between 0.73 and 1.34), thus demonstrating the efficacy of treatment to reduce tinnitus distress (Andersson et al., 2002; Hesser et al., 2012; Jasper et al., 2014; Kaldo et al., 2008). Nyenhuis et al. (2013b) investigated iCBT with minimal contact and reported large effect sizes for the iCBT compared to a control group. In a non-controlled trial within a regular clinical setting, Kaldo et al. (2013) evaluated two parallel interventions in tinnitus patients, that is, iCBT with therapist support and a low-intensity version of iCBT with minimal support. They detected small-to-medium effect sizes for the reduction in tinnitus distress as well as for the alleviation of associated symptoms; they showed that low-intensity iCBT can be promising, in particular for participants with less distress or patients who cannot participate in fully guided iCBT (Kaldo et al., 2013). Although these results are encouraging, there has been no RCT comparing unguided with guided iCBT in conjunction with tinnitus, thus we cannot know whether iCBT with or that without support is more effective for tinnitus sufferers or whether they are equally effective. Previous iCBT studies investigating disorders other than tinnitus yielded mixed results on the influence of therapeutic support on treatment outcome. Whereas several studies provide evidence that therapeutic guidance has an advantageous effect on treatment outcome (Baumeister et al., 2014; Johansson and Andersson, 2012; Palmqvist et al., 2007; Spek et al., 2007; Titov and Andrews, 2008), others obtained no results favoring supported iCBT (Berger et al., 2011; Furmark et al., 2009). Considering these mixed results on therapeutic guidance, one might wonder how much therapist input is actually needed to demonstrate solid improvement after iCBT. This question is difficult to answer when relying on previous research because most of the studies provided fixed amounts of support (e.g., feedback at the end of every treatment week), instead of letting patients choose whether they actually needed support or not. We thus thought it would be worthwhile examining how much support patients would actually request if they could choose, and whether the outcome would differ compared to scheduled support or unguided interventions. One attempt in this direction was made by Berger et al. (2011) in a study on patients with social anxiety disorder. They compared a treatment group whose participants could decide whether they needed additional email and telephone support with an intervention group receiving scheduled weekly support and an unguided intervention group. No significant group differences in any outcome measures were observed, suggesting that unguided treatments are a promising option in the treatment of social anxiety disorder. It is however possible that the amount of support needed differs according to the condition, i.e., patients with social anxiety disorder or insomnia might need less guidance than depressed patients (Andersson, 2014). With regard to tinnitus, patients with significant comorbid disorders such as anxiety, depression, or even personality disorders (Andersson et al., 2004; Erlandsson and Persson, 2006; Zirke et al., 2010; Zöger et al., 2006) might require more support than those with a less disturbing tinnitus and fewer associated problems. We therefore need to take a closer look at the role of scheduled support, support-on-demand, or unguided iCBT.

Patients' outcome expectations might, as previously mentioned, play a crucial role in the efficacy of iCBT in addition to therapeutic support. In traditional face-to-face psychotherapy, we know that outcome expectations are closely related to the treatment's perceived credibility (i.e., how well the treatment is assumed to fit the individual needs; Constantino et al., 2005). Outcome expectations and perceived credibility are usually assessed together via the Credibility Expectancy Questionnaire (CEQ; Devilly and Borkovec, 2000) or the C-Scale (Borkovec and Nau, 1972). Outcome expectations and credibility are being increasingly studied in iCBT research. Studies have detected no relations between credibility/expectations as assessed by the CEQ or C-Scale and reductions in tinnitus distress (Jasper et al., 2014; Kaldo et al., 2008). Further iCBT studies on disorders other than tinnitus showed mixed results regarding the relation between credibility/expectations and outcome (Boettcher et al., 2013; Hedman et al., 2012, 2013). Use of the CEQ or C-Scale does have the drawback that credibility and outcome expectations are often interpreted as one construct, although some suggest that different forms of expectations should be regarded and investigated separately (Devilly and Borkovec, 2000; Greenberg et al., 2006; Schulte, 2008). We therefore think it could prove worthwhile to examine the relation between different forms of outcome expectations (such as hope of improvement, credibility, or fear of change) and actual treatment outcome separately.

As the aforementioned studies reveal, the role of therapeutic guidance and the impact of different forms of outcome expectations on reducing tinnitus distress through iCBT remains unclear. As different studies have proven the general efficacy of iCBT in relieving tinnitus distress, an important next step is to investigate which factors make iCBT work, or in particular which factors are associated with better treatment outcomes. This step is a necessary prerequisite for iCBT's further implementation into regular health care for tinnitus. Accordingly, our study had two major objectives, that is, (1) to examine the impact of therapeutic support in reducing tinnitus distress, and (2) to investigate which kind of patients' expectations are associated with better treatment outcome. We conducted a randomized controlled trial in which tinnitus patients were assigned to an iCBT either receiving support-on-demand or not receiving therapeutic support. Previous findings from iCBT studies for tinnitus led us to predict that the guided iCBT would lead to stronger improvements than the unsupported iCBT. Furthermore, we assumed that higher outcome expectations would be associated with greater reduction in tinnitus distress.

2. Methods

2.1. Participants

Participants were recruited by means of advertisements, articles on websites and in magazines, and via wait lists for participation in an iCBT study on tinnitus. The study's inclusion criteria were: (1) age of at least 18 years; (2) tinnitus lasting over six months; (3) at least mild tinnitus distress (defined by a total score of ≥18 in the Tinnitus Handicap Inventory (THI; Newman et al., 1996) or ≥8 in the Mini-Tinnitus Questionnaire (Mini-TQ; Hiller and Goebel, 2004)); (4) internet access; (5) good knowledge of the German language to read the text; (6) an examination by an otorhinolaryngologist prior to treatment start (assessed by self-report); (7) no psychosis or severe psychological disorder according to the Web-based Screening Questionnaire for Common Mental Disorders (WSQ; Donker et al., 2009); (8) no risk for suicide as assessed by the WSQ; (9) no previous participation in a

similar study; (10) no ongoing psychotherapy for tinnitus; (11) tinnitus as the primary problem (e.g., tinnitus not as a consequence of Menière's disease).

Participants were informed about the study design and the treatment prior to the beginning of the study. All gave their written informed consent. The ethics committee at our site approved the study protocol, and it was registered at www.clinicaltrials.gov (NCT01927991).

2.2. Procedure

Two web pages were set up for the study. One website contained general information about the study and was freely available on the internet. The other website was the treatment portal which included a messaging system; it could only be accessed with a personal study code and password (Andersson, 2014). Tinnitus sufferers interested in participating in our study could answer the Mini-TQ on the information page as a first screening. Patients with at least mild tinnitus distress (≥ 8 in the Mini-TQ) automatically received a link to our study's registration form. After registering, participants could fill in the entire study questionnaire online, which served as the pre-treatment assessment. The questionnaire included questions about demographics, tinnitus characteristics, and study-specific measures including the Tinnitus Handicap Inventory (THI). Participants were also asked about their preferred treatment ("If you were to choose, which treatment (support- or non-support-group) would you prefer?"). The decision on study inclusion was done according to our inclusion and exclusion criteria. In case a cut-off criterion existed, e.g., participants suffered from severe depression or were suicidal (as assessed by the WSQ), they were telephoned in order to conduct further diagnostics. If necessary, the excluded individuals were offered advice and information on how to seek further help. After inclusion, participants were randomly allocated to one of two groups: iCBT with support-on-demand, or iCBT without support (non-support group). Both groups received the same treatment, however, the amount of therapeutic support that was offered varied between groups. The baseline characteristics of participants in both groups did not differ (see Table 1). Randomization was performed by an independent psychologist using an online service which applies a pseudorandom number algorithm (www.randomization.com). Randomization was conducted in two blocks according to the date of registration. Treatment started accordingly at two different points in time (either in October 2012 or in May 2013) and lasted 10 weeks. Participants were randomly assigned to either the support-on-demand or the non-support group at each time point. Post-assessment, which was carried out immediately after treatment, consisted mainly of the same measures as the pre-assessment and included questions on satisfaction with the treatment. An additional telephone interview was conducted one week after the end of treatment. To enhance their compliance throughout the intervention, participants were informed about this interview in advance via email (Andersson et al., 2009). Participants in both groups received the same information about the

Table 1
Sample characteristics.

Characteristics	Support (n = 56)	Non-support (n = 56)	Group differences
Age in years, *M* (*SD*)	51.09 (11.02)	54.14 (12.63)	$t(110) = -1.36$, $p = .176$
Number females, *n* (%)	21 (37.5)	21 (37.5)	$\chi^2(1) = 0.0$, $p = 1.00$
Citizenship, *n* (%)			$\chi^2(2) = 2.16$, $p = .340$
German	53 (94.6)	49 (87.5)	
German & Other	–	1 (1.8)	
Other	3 (5.4)	6 (10.7)	
Highest educational level, *n* (%)			$\chi^2(2) = 0.44$, $p = .978$
No degree	–	–	
Secondary school	23 (41.1)	22 (39.3)	
A-level	11 (19.6)	11 (19.6)	
Academic degree	22 (39.3)	23 (41.1)	
Employment, *n* (%)			$\chi^2(3) = 3.38$, $p = .336$
Employed	38 (67.9)	36 (64.3)	
Unemployed	1 (1.8)	4 (7.1)	
Retired	7 (12.5)	10 (17.9)	
Other	10 (17.9)	6 (10.7)	
Married, *n* (%)	39 (69.6)	38 (67.9)	$\chi^2(1) = 0.42$, $p = .838$
Tinnitus loudness, *n* (%)			$\chi^2(2) = 0.58$, $p = .747$
Slight	1 (1.8)	2 (3.6)	
Moderate	29 (51.8)	31 (55.4)	
Severe	26 (46.4)	23 (41.1)	
Tinnitus duration in years, *M* (*SD*)	9.54 (9.23)	12.51 (12.86)	$t(99.77) = -1.41$, $p = .162$
Hearing impairment, *n* (%)			$\chi^2(3) = 1.44$, $p = .697$
None	11 (19.6)	15 (26.8)	
Slight	26 (46.4)	22 (39.3)	
Moderate	14 (25.0)	12 (21.4)	
Severe	5 (8.9)	7 (12.5)	
Tinnitus distress, *M* (*SD*)			
THI	62.14 (17.41)	57.32 (16.32)	$t(110) = 1.51$, $p = .133$
Mini-TQ	18.00 (3.96)	16.68 (3.82)	$t(110) = 1.80$, $p = .075$
Depressed sympt. (PHQ-9), *M* (*SD*)	10.36 (5.13)	9.52 (4.03)	$t(110) = 0.96$, $p = .338$
Expectation (PATHEV), *M* (*SD*)			
Hope of improvement	15.27 (2.68)	15.04 (2.65)	$t(110) = 0.46$, $p = .646$
Suitability	14.98 (2.69)	14.57 (2.17)	$t(105.24) = 0.89$, $p = .375$
Fear of change	4.14 (1.35)	3.91 (1.13)	$t(110) = 0.98$, $p = .327$
Group preference, *n* (%)			$\chi^2(2) = 0.16$, $p = .921$
Support	29 (51.8)	29 (51.8)	
Non-support	4 (7.1)	3 (5.4)	
No preference	23 (41.1)	24 (42.9)	

Note: THI = Tinnitus Handicap Inventory; Mini-TQ = Mini-Tinnitus Questionnaire; PHQ-9 = Patient Health Questionnaire; PATHEV = Patient Questionnaire on Therapy Expectation and Therapy Evaluation; Hope of Improvement = subscale of the PATHEV; Suitability = subscale of the PATHEV; Fear of Change = subscale of the PATHEV.

post-treatment interview. Follow-up measures were assessed 12 months after treatment. Patients were contacted via email and asked to fill in the questionnaire online, which was the same as the post-treatment questionnaire. Participants who had failed to fill in the online questionnaire after four weeks (during which they were sent two reminders) received the questionnaire and a prepaid envelope via regular mail and were asked to mail it back to us.

2.3. Measures

2.3.1. Primary outcome measures

The Mini-Tinnitus Questionnaire (Mini-TQ; Hiller and Goebel, 2004) and the German version of the Tinnitus Handicap Inventory (THI; Kleinjung et al., 2007; Newman et al., 1996) were used to assess tinnitus distress and severity. Containing 12 items, the Mini-TQ is a shortened version of the well-established Tinnitus-Questionnaire (TQ; Goebel and Hiller, 1992) that proved to be equally powerful as the TQ in detecting improvements during treatment (Hiller and Goebel, 2004). Its test–retest reliability is .89, and its internal consistency for inpatients is Cronbach's $\alpha = .87$, for outpatients it is Cronbach's $\alpha = .90$ (Hiller and Goebel, 2004), in the present study it was Cronbach's $\alpha = .79$. The authors recommend different cut-off scores when classifying tinnitus severity: scores between 1 and 7 indicate clinically relevant tinnitus distress; scores between 8 and 12 are considered as moderate distress; scores between 13 and 18 suggest severe tinnitus distress; and a score above 19 indicates most severe distress.

The THI contains 25 items and is an internationally well-accepted and often used measure in treatment studies on tinnitus (Hesser et al., 2012; Kaldo et al., 2008). It possesses good psychometric properties, having an internal consistency of Cronbach's $\alpha = .93$ (Newman et al., 1996) and a correlation of $r = .70$ with the TQ (Kleinjung et al., 2007). The internal consistency in the present study was Cronbach's $\alpha = .89$. Just as with the Mini-TQ, different levels of tinnitus severity can be classified: scores between 0 and 16 suggest no handicap; those between 18 and 36 indicate mild tinnitus severity; scores between 38 and 56 suggest moderate tinnitus severity; and a score between 58 and 100 is considered as severe tinnitus.

2.3.2. Secondary outcome measures

The German version of the depression scale of the Patient Health Questionnaire (PHQ-9) was used to assess symptoms of depression (Löwe et al., 2002). Each of its nine questions covers one diagnostic criterion of depression according to DSM-IV. With Cronbach's $\alpha = .88$, in the current sample it was Cronbach's $\alpha = .82$, and a correlation with the Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983) of $r = .74$, the PHQ-9 shows good psychometric properties and is an internationally standard measure when evaluating depressive symptoms in medical settings (Gilbody et al., 2007).

To assess the participants' outcome expectations regarding the treatment, we administered the Patient Questionnaire on Therapy Expectation and Evaluation (PATHEV; Schulte, 2005). The PATHEV consists of three subscales with internal consistencies of $\alpha = .73$ ("Fear of Change"), $\alpha = .81$ ("Suitability"), and $\alpha = .89$ ("Hope of Improvement") in the original study. In the present sample, alpha was $\alpha = .62$ ("Fear of Change"), $\alpha = .67$ ("Suitability"), and $\alpha = .82$ ("Hope of Improvement"). The scale "Hope of Improvement" assesses how much the patients believe that the treatment can help them with their problems (e.g., "I believe my problems can finally be solved."). "Fear of Change" addresses the extent to which participants fear negative effects from the therapy (e.g., "From time to time I worry about all the things that will change once my problems have vanished."). The subscale "Suitability" measures how confident patients are that they have found the right treatment (e.g., "I've found the right therapy.").

Satisfaction with treatment was assessed with a measure developed at our site which has not yet been published. It consists of 13 items (e.g., "The self-help met my expectations."), which are answered on a 6-point Likert-scale ranging from "I totally disagree" to "I totally agree". The items load on one factor with loadings between .70 and .93 in the current sample. Internal consistency in the present study was $\alpha = .94$.

2.4. Treatment

Both treatments were based on a manual first used by Andersson et al. (2002) and later updated by Kaldo and Andersson (2004) and Kaldo et al. (2008). It has been translated and modified for use in Germany (for details on the German adaptation see Jasper et al., 2014). The treatment lasted 10 weeks and consisted of 12 mandatory and 6 optional modules which could be downloaded as PDF files via the treatment portal. Treatment modules were assigned individually to each participant and were provided online every week according to each participant's individual treatment plan. Compared to the iCBT previously used (Andersson et al., 2002; Jasper et al., 2014), we added an automated messaging system to the treatment since there is evidence that it furthers treatment completion (Titov et al., 2013). To be able to download the PDF files for the upcoming week, participants had to answer a question about their treatment process by selecting one of three answers (the three answer categories were: (1) "I have evaluated the modules and would like to download the material for the next training week."; (2) "I have not yet evaluated the modules. However, I would still like to download the material for the next training week."; (3) "I have not yet evaluated the modules and would like to download old training materials."). Depending on their answer, participants received an automated email in which they were either complimented for working on the treatment or motivated to do so in the next week. The general content (i.e., complimenting or motivating participants) of the emails was the same every week, but we tried to change the way in which the emails were written to avoid boring patients because that could have made them stop reading the messages. The emails were the same for both treatment groups. The amount of provided therapeutic support differed between the two groups (support-on-demand vs. no support) and is described below.

2.4.1. Support-on-demand

Half of the participants were randomly assigned to the "support-on-demand" condition and hence, to a personal "therapist". The therapist's role was to help participants with the self-help material whenever questions occurred. This contrasts with the normal way support is provided, which usually includes scheduled support within 24 h after submitting the homework (Andersson, 2014). Furthermore, it was the therapist's task to motivate, encourage, and inspire participants to work on the material. Participants could contact their individually-assigned therapist via email to ask for support whenever needed. However, after five weeks of treatment, participants who had not logged into the treatment portal for two and a half weeks were contacted via their private email address and asked whether they were having problems and needed help. The therapists were three advanced psychology students supervised by a licensed therapist with experience in tinnitus treatment.

2.4.2. Non-support

The other half of the participants was allocated to the non-support condition and was also randomly assigned to an individual contact person. In contrast to the personal "therapist" in the support-on-demand group, we call this person an "individual contact person" because he or she could mainly be contacted in case of technical problems. At the beginning of treatment, participants were instructed to work on the treatment themselves and to 'become their own therapist'. Ethical considerations, however, required us to provide therapeutic support in case of a significant deterioration in any of the symptoms or if problems with the training occurred that would have hindered

participants' continuation with the training. We informed participants that they could get in touch with the contact person in such pressing cases. If participants in the non-support condition addressed the contact person, requests were generally answered in a neutral, non-motivating, and non-praising yet friendly manner. In case of questions related to a module's contents, the contact person did not answer the question specifically but rather suggested re-reading the information provided in the module. The contact person gave direct advice only when a) a severe worsening of symptoms was suspected; b) participants asked how to continue after an absence due to illness or holiday, or c) participants wrote that they wanted to end the training. In these cases, participants received precise recommendations on how to proceed.

2.5. Statistical analyses

Prior to recruitment, the sample size was calculated with G*Power (Faul et al., 2007). To reveal a small time x group interaction effect ($f = 0.1, \alpha = 0.05, \beta = 0.8$) the estimated total sample size was $n = 98$. With an expected dropout rate of about 10%, we decided to recruit about 108 patients.

Statistical analyses were performed with the program IBM SPSS 21.0. Baseline characteristics were analyzed using t-tests and χ^2-tests. Since 12.5% of participants did not answer the post-questionnaire, we used a multiple imputation method offered by IBM SPSS 21.0 to estimate missing values on the THI, the Mini-TQ, and the PHQ-9 at post-assessment. By default, this multiple imputation method uses the Markov Chain Monte Carlo (MCMC) method to replace missing data (Asendorpf et al., 2014). To test for differences within and between groups in the aforementioned three measures from pre- to post-treatment, analysis of variances (ANOVA) for repeated measures with the factors time (pre- and post-treatment) and group (support-on-demand and non-support) was carried out followed by paired t-tests with a Bonferroni corrected significance level ($\alpha = .008$). Intra-group and inter-group effect sizes (Hedges' g) were also calculated. Statistically significant changes are not equivalent to clinically relevant changes since they do not provide information about the efficacy of psychotherapy (Jacobson and Truax, 1991). Therefore we calculated clinically significant change for each participant for the THI and Mini-TQ according to the Reliable Change Index (RCI), as defined by Jacobson and Truax (1991). Reliable Change (RC) is calculated by taking into account a patients' pretest (x_1) and posttest (x_2) score as well as the standard error of difference between these two scores (S_{diff}): $RC = (x_2 - x_1) / S_{diff}$. According to the authors, a reliable change of ≥ 1.96 indicates clinically significant improvement, whereas a reliable change of ≤ -1.96 indicates a reliable deterioration (Jacobson and Truax, 1991). In our study, a participant was regarded as clinically significantly improved when attaining an RCI of 1.96 on both measures, that is the THI and the Mini-TQ. Clinically significant change was calculated for completers only.

For follow-up-data at 12 months we analyzed completer data due to a high loss of data from post- to follow-up-assessment. As with the pre- to post-data, we also conducted an ANOVA for repeated measures to test for differences within groups over the three time points (pre, post, follow-up) and between the groups. Again, paired t-tests with Bonferroni corrected significance levels ($\alpha = .006$) were calculated afterwards.

The impact of outcome expectations on treatment outcome was investigated via a linear regression model using the completer data. The change score (pre-treatment − post-treatment) on the THI was entered as the dependent variable in the model. For the data entry, the hierarchical entry method was used as the predictors to select were known from previous research. In a first step, demographic variables (sex, age, tinnitus duration in months, tinnitus loudness according to the Klockhoff and Lindblom rating; Klockhoff and Lindblom, 1967) were entered as predictors in the model. In a second step, the three subscales of the PATHEV ("Hope of Improvement", "Suitability", and "Fear of Change") were entered in the model. Since participants answered the PATHEV before being randomized to either of the two treatment groups and there were no significant differences on the dependent variable between groups, we did not run the regression for the two groups separately. In addition, with the seven

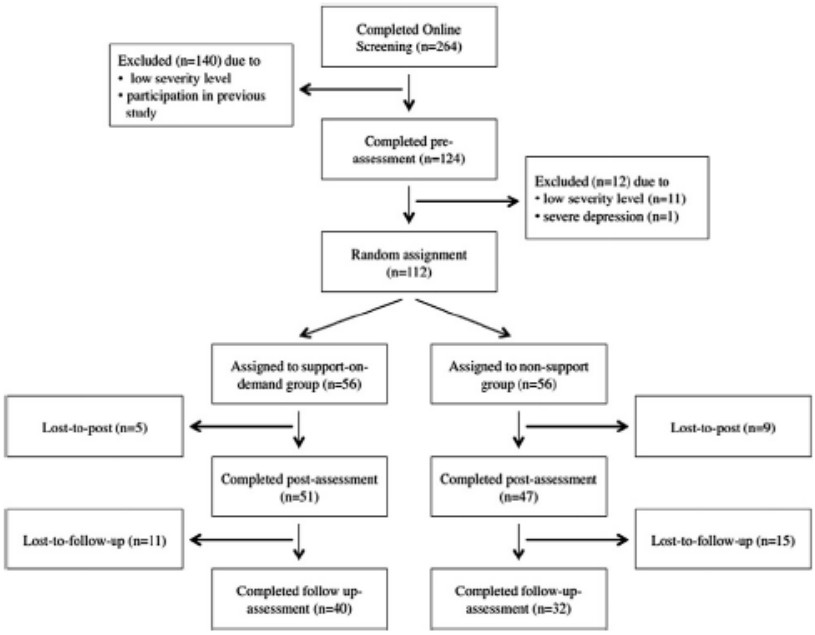

Fig. 1. Flow of participants through the study.

predictors entered in the model, the two groups' sample sizes would have been too small (Field, 2013).

During the whole study, we tried to follow the "Guidelines for Executing and Reporting Internet Intervention Research" (Proudfoot et al., 2011).

3. Results

3.1. Flow of participants and baseline characteristics

As displayed in Fig. 1, of the 264 participants who completed the initial screening, 112 participants met all inclusion criteria and were randomly allocated to one of the two treatment groups.

At the post-assessment, 5 participants in the support-on-demand group and 9 in the non-support group failed to fill in the post-questionnaire, resulting in missing data of 12.5% in total. At follow-up, another 11 support-group patients and another 15 in the non-support group did not fill in the questionnaire, representing a total loss of participants from pre-assessment to follow-up amounting to roughly 36%.

In addition to the missing data, we defined a dropout criterion to specify those participants who did not complete the treatment (but had filled in the post-questionnaire). Participants were regarded as treatment dropouts when they did not log onto the treatment portal anymore during the second half of the treatment time. The rationale for this criterion was based on the fact that to download the majority of the modules, one had to have visited the treatment portal at least once during the second half of the treatment time. With this definition, 9 participants in the support-on-demand group and 11 of those in the non-support group were classified as dropouts, and the difference between groups was not statistically significant ($\chi^2(1) = 0.24$, $p = .622$).

Table 1 displays the demographics, tinnitus-specific characteristics, outcome measures, and group preference at baseline for each group. As the *t*-tests and χ^2-tests show, there were no significant pretreatment differences between the groups in any of the variables. Participants suffered on average from severe tinnitus distress as assessed by the THI and the Mini-TQ. The range of severity at baseline as measured by the Mini-TQ was between 8 and 24, that is, moderate to most severe distress. On the THI the range was 26 to 98, meaning that patients suffered from mild to severe distress.

3.2. Analysis of treatment efficacy and differences between groups from pre- to post-treatment

3.2.1. Primary outcome

Multivariate analyses revealed a significant time effect for overall improvement as measured by the THI and the Mini-TQ ($p \leq .001$). However, contrary to our hypothesis, neither the group effect nor interaction effect for time and group reached significance. Post-hoc tests showed that participants from the support-on-demand and the non-support group improved on the THI and the Mini-TQ (see Table 2). These results show that both groups experienced reduced tinnitus-related distress through the study.

3.2.2. Secondary outcome

The time effect for the PHQ-9 was significant in the ANOVA ($p \leq .001$). Again, we observed neither a significant group effect nor a significant interaction. Additional post-hoc tests revealed that only participants in the support-on-demand group improved significantly on the PHQ-9 (see Table 2), but the lack of interaction suggests that this between-group difference is unreliable.

3.2.3. Effect sizes and clinically significant change

On tinnitus-specific measures (THI, Mini-TQ), both the support-on-demand and the non-support group displayed large within-group effect sizes (Hedges' g between 0.99 and 1.40). The support-on-demand group's effect size on the PHQ-9 was within a small range ($g = 0.47$; Table 2).

Twenty-seven participants (48.2%) in the support-on-demand and 25 participants (44.6%) in the non-support group revealed clinically significant change according to our criterion of having an RCI of at least 1.96 on the THI and the Mini-TQ. The difference between groups was not significant ($\chi^2(2) = 1.31$, $p = .52$). Furthermore, both groups' mean scores on the THI and Mini-TQ at the start of treatment were in the range indicating severe tinnitus distress. After the end of treatment, means of both groups improved to the range indicating moderate tinnitus distress on both measures. Two participants showed clinically significant deterioration on the Mini-TQ and two on the THI. No participant presented clinically significant deterioration on both of the measures.

3.3. Analysis of treatment efficacy and differences between groups from pre- to post-treatment to follow-up

3.3.1. Primary outcome

The ANOVA for repeated measures testing for differences between pre-, post-, and follow-up-assessments between the two treatment groups on the THI and Mini-TQ revealed a significant time effect in the multivariate analyses ($p \leq .001$). Contrary to our hypothesis, however, neither the interaction nor group effect revealed any significant results, thus no significant differences between groups existed. According to Mauchly's Test of Sphericity, the assumption of sphericity was violated for the univariate analyses. Degrees of freedom were therefore corrected according to Greenhouse–Geisser. Univariate analyses showed that the differences are significant for the THI and Mini-TQ (see Table 3). Additional post-hoc *t*-tests investigating within-groups differences revealed that differences between the pre- and post-assessments as well as those between pre-assessment and follow-up were

Table 2
Treatment outcome at post-assessment: Means, F- and t-statistics, and effect sizes.

			Within groups			Between groups		
	Pre *M* (*SD*)	Post *M* (*SD*)	Time effect	Pre–Post	ES (95% CI)	Group effect	Interaction	ES (95% CI)
THI			$F(1, 110) = 118.00^{**}$			$F(1, 110) = 1.04$	$F(1, 110) = 1.27$	0.05 (−0.32, 0.42)
Support	62.14 (17.41)	41.33 (19.17)		$t(55) = 7.51^{**}$	1.13 (0.73, 1.53)			
Non-support	57.32 (16.32)	40.36 (17.71)		$t(55) = 7.68^{**}$	0.99 (0.60, 1.38)			
Mini-TQ			$F(1, 110) = 159.59^{**}$			$F(1, 110) = 2.74$	$F(1, 110) = 0.24$	0.19 (−0.19, 0.56)
Support	18.00 (3.96)	11.75 (4.86)		$t(55) = 8.24^{**}$	1.40 (0.99, 1.81)			
Non-support	16.68 (3.82)	10.86 (4.68)		$t(55) = 8.46^{**}$	1.35 (0.94, 1.76)			
PHQ-9			$F(1, 110) = 15.07^{**}$			$F(1, 110) = 0.11$	$F(1, 110) = 1.76$	0.07 (−0.44, 0.30)
Support	10.36 (5.13)	8.02 (4.82)		$t(55) = 3.52^{**}$	0.47 (0.09, 0.84)			
Non-support	9.52 (4.03)	8.38 (5.11)		$t(55) = 1.54$	0.25 (−0.13, 0.62)			

Note. n = 56 in each group; ** = p < .001; ES = effect size (Hedges' g); CI = Confidence Interval; THI = Tinnitus Handicap Inventory; Mini-TQ = Mini-Tinnitus Questionnaire; PHQ-9 = Patient Health Questionnaire.

Table 3
Treatment outcome at post-assessment and follow-up: Means, F- and t-statistics.

				Within groups			Between groups		
	Pre *M* (*SD*)	Post *M* (*SD*)	FU *M* (*SD*)	Time effect[a]	Pre–Post	Pre–FU	Post-FU	Group effect[a]	Interaction
THI				F(1.63, 69.37) = 85.74**				F(1.63, 69.37) = 0.58	F(1, 70) = 0.06
Support	60.85 (17.32)	38.80 (20.36)	37.05 (20.48)		t(39) = 6.39**	t(39) = 7.57**	t(39) = 0.88		
Non-Support	58.50 (16.65)	35.88 (19.30)	33.25 (22.90)		t(31) = 8.30**	t(31) = 7.40**	t(31) = 1.17		
Mini-TQ				F(1.80, 69.20) = 101.01**				F(1.80, 69.20) = 1.49	F(1, 70) = 0.42
Support	17.68 (3.94)	11.58 (5.04)	9.98 (5.27)		t(39) = 6.93**	t(39) = 8.76**	t(39) = 2.56		
Non-Support	16.59 (4.06)	9.84 (4.87)	9.28 (6.00)		t(31) = 8.57**	t(31) = 8.37**	t(31) = 0.82		
PHQ-9				F(1.81, 69.19) = 32.39**				F(1.81, 69.19) = 0.53	F(1, 70) = 1.76
Support	9.85 (4.70)	6.80 (4.17)	6.35 (4.48)		t(39) = 4.25**	t(39) = 5.03**	t(39) = 0.85		
Non-Support	9.06 (4.35)	6.78 (4.67)	5.17 (4.72)		t(31) = 3.22*	t(31) = 5.22**	t(31) = 2.89		

Note. n = 40 in the support group; n = 32 in the non-support group ** = p < .001; FU = follow-up; THI = Tinnitus Handicap Inventory; Mini-TQ = Mini-Tinnitus Questionnaire; PHQ-9 = Patient Health Questionnaire; [a] degrees of freedom have been corrected according to Greenhouse–Geisser.

significant in both groups (see Table 3). No significant differences between the post-assessment and follow-up were observed, demonstrating that improvements in both measures were stable from the post- to follow-up-assessment.

3.3.2. Secondary outcome

The time effect for the PHQ-9 was significant in the ANOVA. Again, the group effect and interaction revealed no significant differences, thus no significant differences between groups existed. Post-hoc *t*-tests addressing within-groups differences showed that differences in both groups from the pre- to post-assessment and from the pre- to follow-up-assessment were significant on the PHQ-9. No significant differences between the post- and follow-up assessments were apparent, indicating that improvements in the PHQ-9 were stable from the post- to follow-up assessment.

3.4. Expectation as a predictor of treatment outcome

We hypothesized that patients' positive outcome expectations would be associated with greater reductions in tinnitus distress. Of the demographics entered in the regression model, only tinnitus loudness was a significant predictor of treatment outcome ($\beta = 0.21$, $p = .046$), meaning that louder tinnitus at treatment start predicted improvement. Of the three PATHEV subscales, "Hope of Improvement" predicted treatment outcome significantly ($\beta = 0.28$, $p = .027$, see Table 4) at post-treatment, indicating that being more optimistic of improvement at the start of treatment leads to greater treatment efficacy and thus to significantly lower levels of tinnitus distress at the end of treatment. Contrary to our hypothesis, neither the treatment's perceived suitability nor fear of change predicted treatment outcome.

3.5. Further analyses

3.5.1. Treatment preference and satisfaction with treatment

We analyzed which of the two groups was the preferred treatment option at pre-assessment and how satisfied participants were with the treatment at post-assessment. Prior to treatment, 51.8% of participants preferred the support-on-demand group over the non-support group (6.2%), whereas 42.0% expressed no preferences. At the post-assessment there was no significant group difference in satisfaction with treatment as assessed by the self-developed measure ($t(86) = 0.22$; $p = .822$).

3.5.2. Number of messages from patients

Below we describe calculations of the messages the patients sent. Calculated were all the messages sent by patients, both those containing therapeutic requests and messages requesting technical support, or about arranging an appointment for the post-treatment interview. The support-group participants sent 224 messages throughout the treatment, or 4 messages ($SD = 0.53$) per patient throughout treatment ($MD = 3$, range 0–22). Eight participants in the support-on-demand group (14%) never sent a message. The non-support group participants also sent messages asking for technical support and containing questions about treatment contents despite having been advised not to. The non-support group participants sent 109 messages, equaling an average of 1.95 ($SD = 0.26$) messages per patient throughout treatment ($MD = 1$, range 0–8). Fifteen of the non-support group participants (26.8%) never sent a message. The number of messages sent differed significantly between groups ($t(80.34) = 3.46$; $p \leq .001$); the number of those who never sent a message did not differ between groups ($\chi^2(1) = 2.13$; $p = .144$). Initial tinnitus distress as assessed by the THI and number of messages sent did not correlate significantly ($r = .113$; $p = .234$), nor did we observe any association between the number of messages sent and treatment outcome as assessed by the difference score (pre − post) in the THI ($r = .138$; $p = .175$).

Table 4
Expectation as a predictor of outcome.

Step	Predictor	B	SE	β	p	R^2	Change in R^2	F	p
1						.05	.05	1.31	.274
	Sex	3.14	3.87	0.08	.419				
	Age	0.16	0.19	0.09	.417				
	Tinnitus duration	−0.01	0.02	−0.04	.727				
	Tinnitus loudness	5.94	3.71	0.17	.113				
2						.18	.13	4.59	.005
	Sex	3.68	3.69	0.10	.321				
	Age	0.04	0.19	0.02	.845				
	Tinnitus duration	−0.001	0.01	−0.01	.953				
	Tinnitus loudness	7.14	3.53	0.21	.046				
	PATHEV—Hope of Improvement	1.91	0.85	0.28	.027				
	PATHEV—Suitability	1.13	0.94	0.15	.233				
	PATHEV—Fear of Change	2.05	1.48	0.14	.169				

Note. n = 98; dependent variable = change score from pre- to post-assessment on the Tinnitus Handicap Inventory; SE = standard error; PATHEV = Patient Questionnaire on Therapy Expectation and Evaluation.

3.5.3. Time spent by therapist

We calculated the time the therapist spent on each participant throughout the treatment (irrespective of group allocation). In the first step, just the therapeutic time (answering messages, training or supervision on how to answer messages) spent per patient was calculated separately for each group. In the support-on-demand group, therapists spent on average 36.18 min ($SD = 83.68$) on each participant over the entire treatment duration, on average 3 min and 36 s of support per patient every week. As we noted wide divergence in the amounts of support demanded throughout the treatment by participants in the support-on-demand group (range 0 to 541 min), we investigated whether the support demanded was related to initial tinnitus severity, but detected no significant correlation ($r = .023$; $p = .806$).

Concerning the non-support group, therapists spent on average 6.62 min ($SD = 9.59$) answering emails over the entire treatment period, equaling 42 s per patient per week on average. The average time spent supporting each participant differed significantly between the two groups ($t(56.45) = 2.63$; $p = .011$), that is, more time per patient was spent in the support group. Therapeutic time was not related to treatment outcome as determined by the difference score on the THI ($r = -.068$; $p = .507$).

In the second step, time spent per patient with the purpose of providing technical support was calculated for each group separately. In the support-on-demand group, therapists spent on average 2.93 min ($SD = 6.00$) per patient providing technical support during the entire treatment. In the non-support group, 2.70 min ($SD = 5.65$) were spent. The difference between groups was not significant ($t(110) = .211$; $p = .833$). In addition, there was no correlation between time spent on technical support and treatment outcome on the THI ($r = 0.09$; $p = .396$).

4. Discussion

Our study shows that iCBT is effective in reducing tinnitus-related distress in patients suffering from tinnitus. However, contrary to our hypothesis, we could not demonstrate that the on-demand guidance provided by iCBT led to greater improvements than the unguided iCBT. Positive treatment expectations in the form of hope of improvement did however predict better outcome regarding tinnitus distress.

Our finding that both the support-on-demand and the non-support groups revealed similar improvements is somewhat surprising. However, previous studies on the role of therapeutic support in iCBT also reported mixed results. For example Berger et al. (2011) found that guided self-help for social anxiety disorder was not superior to unguided iCBT, whereas Baumeister et al. (2014) provided evidence that internet-based interventions including therapeutic guidance yielded better results than interventions without guidance. Similarly, some argue that at least minimal therapist contact is one of the most important aspects of successful outcomes in iCBT (Andersson et al., 2013). Several reasons for both groups' good improvements are conceivable. First, the treatment program had a fixed endpoint that was 10 weeks after the start of treatment, meaning that the program was available online only up to a specific deadline. According to Andersson et al. (2009), a fixed deadline is an important aspect in treatment efficacy that might even reduce the need for therapeutic support. Second, as Andersson et al. (2009) recommended, we included a post-treatment interview to enhance overall treatment compliance. They argued that if progress in treatment is expected and evaluated in a post-treatment interview, compliance might increase. Although we did not explicitly ask participants to describe their treatment's progress, but rather their satisfaction with treatment, they knew that we were expecting feedback from them about the treatment in the post-treatment interview. This fact also may have kept the non-support group participants motivated to work on the treatment and hence led to their good treatment outcome. Third, we included automated emails in the treatment with the aim of motivating participants to work on the treatment. Although the therapists did not send these emails personally and patients were not addressed personally, participants received at least some feedback every week, a factor known to facilitate treatment completion (Titov et al., 2013). Fourth, all participants knew from the beginning that treatment was being carried out by psychologists who could be contacted in urgent cases. This knowledge may also have had a positive impact on treatment outcome.

Another interesting aspect regarding our results is the low amount of support that was actually requested by the support-on-demand group. In contrast to previous studies that administered the same self-help program in tinnitus-sufferers (e.g., Jasper et al., 2014), the therapeutic support was not scheduled to take place on a specific date. This implied that participants could ask whenever and for as much support as they wanted, but they were not obliged to ask for support or to send any feedback. Jasper et al. (2014) reported an average therapist's time-spent-per-patient-per-week of 13.76 min. This stands in contrast to the support-on-demand group's 3.36 min per week and patient. Despite this difference in therapist time, the numbers of clinically significant improvement (support-on-demand group: 48%; non-support group: 44%) are comparable to those in Jasper et al.'s study (41%). This indicates that self-help in tinnitus sufferers can be effective even when little therapist support is provided, revealing the potential of offering iCBT with minimal therapeutic contact.

In our study, positive expectations in the form of hope of improvement were a predictor of treatment success. For future internet-delivered treatments, this means that it could be advantageous to raise patients' expectations regarding treatment outcome prior to the start of treatment in order to enable greater improvement. But how are positive outcome expectations like hope of improvement induced?

In conjunction with pharmacological treatment, some suggest that providing information on the expected drug effect positively influences beliefs about outcome (Bingel, 2013). With iCBT, this might mean that providing information on the efficacy of the treatment being offered, for example by presenting study results or satisfaction ratings from patients who have already completed therapy, could enhance improvement. Furthermore, it might be important to inform patients about the clinicians conducting the treatment to boost positive expectations regarding treatment outcome and thus to enhance treatment efficacy. Participants might experience greater hope of improvement if they are made aware that well-trained CBT-professionals with substantial experience in the field will be treating them. This might apply to tinnitus sufferers especially, as they often have long histories of (unsuccessful) treatment attempts (Pilgramm et al., 1999) and might thus have little initial hope of improvement.

Nevertheless, expectations in the form of perceived suitability and fear of change failed to predict treatment outcome. One explanation for the missing relationship between treatment outcome and perceived suitability might be that we had asked for the perceived suitability prior to the start of treatment and randomization, thus the participants were only able to rate the suitability at that time according to theoretical information and not by personal observation or experience (Schulte, 2008). Our results may have been different had we asked that question after two weeks of treatment. Furthermore, the rather low internal consistencies displayed by the subscales "Suitability" and "Fear of Change" ($\leq .70$) in our sample lower the value of the regression analysis' results (Cicchetti, 1994; Rosenthal, 1994).

Several study limitations should be noted (1) Although we only lost 12.5% of participants for post-assessment, our results are compromised by the fact that we lost 36% of participants for follow-up. It is possible that only those participants satisfied with the treatment answered the post-/follow-up-questionnaires. Our follow-up results must therefore be considered with particular caution. (2) As is true for many internet-delivered treatments, the sample is selective, that is, only participants having access to a computer and internet, and those with adequate reading skills and sufficiently motivated to work on the self-help program on their own were eligible for the study. In addition, perhaps only those tinnitus sufferers willing to work on a treatment without support participated in our study. Prior to the start of treatment and study registration, patients were told that their chances of being assigned to the non-support group were 50%. In addition, our sample consisted of participants with a high education level, as 40% earned an academic degree; that limits the generalizability of our results. (3) The severity of tinnitus distress in our sample was rather high compared to other studies (Jasper et al., 2014; Kaldo et al., 2008). As it is easier to achieve improvements in individuals complaining of greater initial tinnitus distress, this fact may partly account for the high within-group effect sizes detected in our study. (4) Another limitation concerns the fact that the non-support group may have been offered too much therapeutic and technical support. For example, the post-treatment interview (conducted in both groups) could be regarded as a kind of therapeutic support. Furthermore, therapists, rather than mere IT personnel, provided the technical support. The therapists may have answered in an overly-therapeutic manner, or the participants perceived even technical support as being very supportive and helpful. In a future study, it would thus be necessary to a) recruit a control group not receiving any kind of support, b) provide technical support via technical staff, and c) assess more precisely why some patients used the support-on-demand intensively whereas others rarely did. (5) Finally, another limitation of the present study is the fact that we did not assess negative effects with a validated outcome measure or an interview as recommended by Rozental et al. (2014). This would have been important to better understand why and how negative effects occur in order to minimize them in future treatments. This might have been particularly useful in the present study because of the difference in support offered, which could make a difference in experiencing negative effects (Rozental et al., 2014).

Despite its limitations, our study results constitute a good starting point for further research on iCBT. It is important that the impact of therapeutic support on the efficacy of iCBT be examined in order to build a case for the evidence-based implementation of iCBT within standard healthcare. For example, to test the amount of support needed, various factors could be included stepwise in a non-support condition (e.g., post-treatment interview, automated emails, or fixed deadline). In addition, the observation that positive outcome expectations in the form of hope of improvement can exert a beneficial effect on treatment outcome is important. Future research should investigate how outcome expectations can be improved prior to the start of treatment in iCBT for tinnitus patients, but in other patient cohorts as well. Moreover, it is essential to discover other predictors of treatment outcome in order to optimize iCBT interventions and to identify the initial steps that need to be taken to tailor iCBT for individual needs.

To the best of our knowledge, this study is the first to have systematically investigated the roles of 'on-demand' therapeutic guidance and of different aspects of outcome expectations in conjunction with reducing tinnitus distress in iCBT. We have demonstrated the efficacy of an internet-delivered treatment in reducing tinnitus-related distress, even when no support is provided. In addition, even when patients are offered the option of requesting support, much less time needs to be invested than during face-to-face therapy. This underlines the cost effectiveness of internet-delivered treatments. Our results confirm that iCBT can be a good option for the treatment of tinnitus patients, especially when face-to-face therapy is unavailable. With our study we have made one attempt to investigate predictors of treatment outcome in iCBT — an important step in improving internet-delivered treatments.

Conflict of interest

The authors declare no conflict of interest.

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A.3 Studie 3

Patients' attributions regarding negative effects of psychotherapy: Qualitative interviews with an affected group

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Abstract

Objective: The current study aimed at identifying negative effects of psychotherapy and their origins through patient interviews. Method: Twenty-four former psychotherapy patients who had experienced negative treatment effects were interviewed. Recordings were transliterated and analysed by means of qualitative content analysis. Categories for underlying similar topics were developed, quantitatively analysed by means of frequency analysis, and incorporated in two systems of categories: one for areas of negative effects and one for the perceived origins of negative effects. Results: Altogether, we identified 127 negative effects grouped into 15 categories representing different areas of patients' lives. The origins patients reported for these effects could be allocated to four main categories with different subcategories. Of the four main categories, *reasons for negative effects of an appropriate therapy* was most frequently used (43.8%), followed by *problems in the therapeutic relationship* (25.4%), *reasons for negative effects due to unprofessionally performed therapy* (19.4%), and *malpractice and unethical behaviour* (11.4%). Conclusions: Negative effects of psychotherapy affect different areas of patients' lives. They occur after therapeutic misconduct but also after *lege artis* therapies. It is necessary to determine which negative effects can be avoided and which must be considered an inherent part of the treatment process.

Keywords: Psychotherapy research, negative treatment effects, adverse effects, side effects, unethical therapist behaviour, therapeutic malpractice

Introduction

Negative effects of psychotherapy have long been overlooked within effectiveness research and have only recently been addressed in empirical studies (Haupt & Linden, 2011; Ladwig, Rief, & Nestoriuc, 2014; Lambert & Ogles, 2004). They occur in different areas of patients' lives (Ladwig et al., 2014) and therapists often assume that negative effects are part of successful treatment ("no pain, no gain"). This point of view was refuted by a recent study, demonstrating that adverse effects of psychotherapy lead to less successful therapies in patients suffering from obsessive compulsive disorder (Moritz et al., 2015). It reinforces the need to reduce negative effects to a minimum and therefore makes it essential that we better understand what kinds of negative effects occur and where they originate.

When it comes to negative experiences of psychotherapy, different phenomena are described and different terms are used, e.g., symptom deterioration (Bergin & Lambert, 1978), side effects (Hoffmann, Rudolf, & Strauß, 2008), therapeutic malpractice (Emmelkamp & Foa, 1983), and unwanted effects (Haupt & Linden, 2011). To avoid overlooking any effects patients experience, we refer in this study to a broad definition of negative effects (see also Ladwig et al., 2014).

> *Negative effects of psychotherapy (NEP) are changes in all areas of a patient's "well-being" that are perceived as negative and cause direct or indirect harm to the patient. These changes can occur during, immediately after, or sometime after the psychotherapeutic treatment. Patients view the cause of this negative effect in the treatment and not in other external influences. Additionally, if the therapy was conducted lege artis and that has been verified by the therapist and/or objective independent raters, NEP can be further classified as side effects of psychotherapy. Malpractice and unethical behavior (MUB) are*

associated with negative effects in the sense that they are perceived as negative and cause direct or indirect harm to the patient. However, they are not characteristics of lege artis psychotherapy.

Little is known about the incidence and prevalence of NEP. The few existing empirical studies state that 2 to 10% of patients report symptom deterioration or negative effects during or after treatment (Crawford et al., 2016; Jacobi, Uhmann, & Hoyer, 2011; Lambert & Ogles, 2004). In an online-based study (Ladwig et al., 2014), we investigated NEP and MUB in all areas of patients' lives and discovered that almost all former psychotherapy patients reported at least one NEP they attributed to treatment. The most frequent NEP patients reported were in the field of intrapersonal changes (e.g., things had not been going well for longer periods since the end of therapy) and in the field of stigmatisation (e.g., patients had difficulty obtaining insurance). Our results confirm that symptom deterioration is only one aspect of NEP, a finding consistent with the aforementioned broad definition of NEP. Nevertheless, frequency alone cannot provide insight into the origins of these effects and which aspects of the psychotherapeutic treatment facilitate their occurrence. An approach that could complement these initial, worthwhile studies on the frequency of NEP is qualitative research (see for example Fossey, Harvey, McDermott, & Davidson, 2002). Its methods provide a valuable source of information to gain deeper understanding of individual patients' experiences, perceptions, and the mechanisms that result in NEP.

Various researchers have started identifying the origins of NEP and have tried to categorise them. However, no clear distinction between the effects themselves and their origins has been made, nor has a systematic assessment been carried out (Kaczmarek et al., 2012; Lieberei & Linden, 2008). A system of categories clearly targeting the origins of NEP and based on their clinical experience was proposed by Hoffmann, Rudolf, &

Strauß (2008). They propose four categories: the first refers to *lack of success or side effects of an appropriate therapy*, meaning that the therapy was carried out according to the guidelines but negative effects occurred anyway. The second category is *lack of success or side effects due to unprofessionally performed therapy*, meaning that the therapy's indication and technique were generally correct but the therapist had violated therapeutic base variables. *Lack of fit („mismatching") between the personalities of the therapist and patient* is the third category in Hoffmann et al.'s system and refers to cases in which the patient and therapist are both suitable for treatment but that the two together do not combine well or "fit". In the last category, *damage due to unethical therapist behaviour*, any of the therapist's behaviours are categorised that violate ethical principles and hence lead to negative effects. This category is equal to MUB, as proposed in the definition of NEP described above and indicates that MUB can lead to NEP. In our study we refer to Hoffmann et al.'s classification since it attempts to provide an all-encompassing system for the origins of NEP.

Nevertheless, as no evaluation of these origins has been conducted so far, we made it the focus of this study. Most of the literature on NEP, and attempts to categorise them are based on theoretical frameworks or case reports and personal experiences by therapists or clinicians, but not by those affected, namely the patients (Berk & Parker, 2009; Hoffmann et al., 2008; Lieberei & Linden, 2008). Even when therapy outcomes are evaluated from a patient's perspective, this is often done within pre-defined categories using quantitative methods, e.g., via questionnaires or structured interviews that leave no room to gather further information, and most clinical trials in psychotherapy do not assess NEP at all. As mentioned previously, a qualitative approach might overcome such problems and has already been successfully applied in categorising negative effects of internet-based treatments (Rozental, Boettcher,

Andersson, Schmidt, & Carlbring, 2015). Thus, being based on patient interviews, in this study we attempt to determine the specific factors patients hold responsible for the development of NEP and whether these can be grouped into meaningful categories in order to better understand how NEP might develop. We aimed to answer the following questions:

(1) Which kind of NEP are reported by a sample of affected psychotherapeutic patients? (2) What are the subjective origins to which patients attribute these NEP? (3) Can these attributions be categorised according to the system proposed by Hoffmann et al.?

Methods

The reporting follows the COREQ-Checklist (Consolidated Criteria for Reporting Qualitative Research; Tong, Sainsbury, & Craig, 2007).

Participants

We interviewed 24 former psychotherapy patients (18 women, 6 men) aged between 21 and 60 years (M=39.9, SD=12.4). Table 1 illustrates their socio-demographics. Most were treated in an outpatient setting (58%). Therapy duration ranged from just a few sessions to more than 300 sessions, and was completed on average 4.1 years ago (SD = 4.5, range: 3 months – 17 years). When asked about their therapist's approach, eight patients named psychoanalysis, four reported having been in cognitive behavioural therapy, another four reported having undergone a psychodynamic approach; three patients named other therapeutic approaches ("body-oriented therapy", "integrative therapy", "transactional analysis"). Five patients could not name their therapist's approach.

- Enter Table 1 here -

Patients' reasons for seeking treatment ranged from general overload and stress to actual psychological diagnoses (depression, PTSD, anxiety, eating disorders, etc.).

Table 2 provides an overview of all self-reported reasons for seeking psychological treatment.

- Enter Table 2 here -

recruitment. Participants were recruited from a previous study's cohort validating a new instrument online: the Inventory for Negative Effects of Psychotherapy (INEP; Ladwig et al., 2014). The present study's inclusion criteria were the patients' having experienced NEP, being cognitively fit, at least 18 years of age, and able to understand and speak German. 109 participants provided informed consent to be re-contacted for a follow-up study involving a telephone interview. Participants who had reported at least two NEP (n = 95; 14 participants reported none or only one NEP and were excluded from further analyses) were selected as potential participants and sent an information sheet about the study as well as an informed consent form via email. Patients interested in participating sent their phone number and the signed informed consent in separate emails. Altogether, 33 individuals agreed to study participation (61 did not respond to the email invitation and one email address was incorrect) and finished their interviews. Of the 33, five participants were part of training interviews and four experienced negative effects that could not be clearly attributed to the psychotherapeutic treatment and were hence excluded from data analysis. Ultimately, 24 participants were included in our data analysis. For having participated in the study, patients were offered a gift certificate worth 5 Euros for an e-commerce company.

Interview Protocol

The interview design was based on the INEP (Ladwig et al., 2014) and consisted of four open and eight closed questions for each negative effect. Patients were asked to refer to one psychotherapeutic experience only. In the beginning, participants were queried about their previous psychotherapy (setting, theoretical background, time frame, etc.).

They were then asked about possible NEP in eleven set categories addressing areas of life in which NEP might have occurred. These categories were developed based on the INEP (Ladwig et al., 2014). In order not to overlook any areas of life in which NEP might have occurred, participants were asked to openly name other areas and were then interviewed about them. For every change they indicated, participants first had to report whether the change was experienced as negative and where they think it originated. Afterwards, they had to answer questions about the therapy in general. In case the interview was overly emotional for the patients, they were able to stop the interview at anytime and/or be put in contact with a trained psychotherapist (IL or YN). Patients were interviewed only once.

Data Collection

Interviews were conducted via the software "Skype" and recorded (with patients' consent) with "Call Graph". At the beginning of the interview, participants were again informed about the procedure and could pose questions. The interview was conducted according to a script by a female advanced clinical psychology master student. She conducted five interviews as training in advance (under the supervision of IL and YN) and had had no prior relationship with the patients. Interviews lasted between 41 and 153 minutes, and were carried out over a three-month period in the spring of 2012. The mean duration of the interviews was one hour and eleven minutes (SD: 28 minutes). No notes were taken during the interviews, however, important impressions were written down after the end of each interview. After the end of data collection, participants were offered a transcript of their interview.

Ethical approval for this study was obtained from the local ethics committee, Department of Psychology, Philipps-University Marburg, Germany.

Data Analysis

To examine which NEP patients experience and where and how they thought these NEP originated, qualitative data was collected and then analysed using Mayring's structuring qualitative content analysis (Mayring, 2010). Quantitative data (sociodemographic and clinical variables) were analysed statistically using SPSS Version 21 and Microsoft Excel Version 15.

transcription. The interviews were transliterated with "f4 plus" according to a guideline previously designed by our research team and based on guidelines according to Dresing and Pehl (2012). All interviews were transcribed by three graduate students in clinical psychology, one of them being the initial interviewer. Then, the entire research team compared and rechecked the transcripts to identify and correct potential inaccuracies. The research team consisted of three graduate students (two female and one male), one PhD candidate (IL, female), and one senior researcher (YN, PhD, female). The PhD candidate underwent special training to become a psychotherapist, the senior researcher is a licensed psychotherapist and experienced in patient care. Once this process was finished, the team agreed upon a transcript for each interview, which formed the basis for coding the material.

development of a system of categories concerning negative effects of psychotherapy and their origins from the patients' perspective. According to structuring qualitative content analyses as proposed by Mayring (Mayring, 2010) we analysed the qualitative material step by step, broke it down into content analytical units (sentences or just words) and then assigned those to categories and subcategories (coded) - common themes within the interviews. The goal was to filter out an underlying structure of the material and create a system of categories. Content analytical units were coded to previously-defined categories (empirically driven, deductive) or

newly-discovered categories (data-driven, inductive). To achieve this, guidelines for the coding process had been formulated within a coding agenda including key examples, with rules for coding in each separate category. If necessary, the system of categories was re-examined and revised; this necessitated a reappraisal of the material. Revisions of the system of categories or implementation of new categories underwent several feedback loops within the research team. Disagreements were discussed and resolved by consensus. All interviews were independently coded by each graduate student. The interview transcripts were coded using MAXQDA 10 (VERBI Software Consult., n.d.).

Concerning NEP, eleven categories had been established in accordance with a previously-generated questionnaire (see section "Interview Protocol"), and those formed the basis for the coding agenda. Any additional NEP that failed to fit within the established categories were assigned to inductively-developed categories and added to the coding agenda. A NEP was determined according to the following definition: (1) a change had to be experienced as negative by the participant and (2) this had to have been found subjectively stressful either during or after treatment. After several analyses and restructuring rounds, the coding system for NEP consisted of fifteen main categories.

Regarding potential origins of NEP, a coding agenda was generated from the model by Hoffmann and colleagues (2008). If attributions concerning the origins of NEP did not fit within this agenda, the content of a category was adjusted and these modified categories then incorporated within the coding agenda. After several analyses and restructuring rounds within the research team, the coding system for the origins of NEP revealed four modified main categories as compared to Hoffmann and colleagues (see below for detailed description). Ongoing verbal and written exchanges among research team members ensured validity as well as reliability. Furthermore, we calculated the

commonly used reliability index Cohen's kappa from all three raters' codings. We achieved intercoder reliability of $\kappa = .73$, indicating good reliability for qualitative projects. In addition, we analysed quantitative properties such as each category's base rates.

Results

Occurrence and Categories of Negative Effects

All in all, 127 NEP were reported ranging from one to ten effects per patient, with a mean of five NEP (SD = 2.3) per patient. The most frequently reported NEP corresponded to the categories *therapeutic relationship* (k = 18), *existing symptoms* (k = 18), and *new symptoms* (k = 14), see also Table 3.

- Insert Table 3 -

NEP occurred in all eleven established categories (*existing symptoms, new symptoms, problems in the therapeutic relationship, reduced ability to cope with stress, reduced ability to relax, more conflicts in partnership, worse relationship with family, worse relationship with friends, stigmatisation, dependence on therapist, dependence on therapy)* as well as in several other areas, which were then analysed and subsumed in four new categories by referring to the qualitative content analysis. These four new categories were *negative change in personality*, *difficulty trusting others*, *fragile self-concept*, and *lack of complacency* (see also Table 3). Figure 1 shows the number of NEP per category.

- Enter Figure 1 here -

Patients' attributions regarding the origin of negative effects

Since it was possible to name more than one origin for each negative effect, the patients reported 299 origins for the 127 NEP. We identified four main categories for these 299 attributions (see also Table 4). Within the main categories, 25 subcategories were

derived.

- Enter Table 4 here -

Category 1: Reasons for negative effects of an appropriate therapy. The first category summarises origins for NEP from therapeutic treatments the patients regarded *lege artis*. Each participant yielded at least one coding in this category; a total of 131 codings were reported. We identified eight subcategories (see also table 4):

(1) *Characteristics of patients' environment* encodes origins that are not specific to treatment like the health care system, family problems, and stigmatisation.

(2) Origins such as the psychological disorder, specific symptoms, patients' own standards, and lack of cooperation on the part of the patient were coded as *characteristics of the patient*.

(3) In the subcategory *characteristics of the therapeutic setting* origins such as the therapist's gender, time spent in therapy, and required effort are summarised.

(4) Patients who reported being dependent on the therapy or who focused too intensely on the therapy are allocated to *dependency on therapist or therapy*.

(5) *Not the right therapy/technique* means that patients found the theoretical background or interventions unsuitable for solving their problems, as a citation from one patient shows (patient ID in brackets):

> "I trace it back to this classical psychoanalysis setting; […] the kind man just sitting behind me and not reassuring me […]." (#017)

(6) The fact that new problems might become apparent during therapy is summarised in the subcategory *therapy as a process that reveals and changes things*. One patient for instance said:

> "[…] for the first time, certain things stood out or became clear that hadn't been […] noticed before, […]" (#014)

(7) In case the therapy was unsuccessful or symptoms deteriorated, this was allocated to *lack of success and deterioration*:

> "Yeah, because I couldn't make any progress." (#026)

(8) *Characteristics of the clinical setting* refers to features of the treatment facility, i.e., when a patient's request for a change of therapist is not granted.

Category 2: Problems in the therapeutic relationship. Originally Hoffmann and colleagues postulated a category referred to as a „mismatch" between the personalities of the therapist and patient; however this category was identified as only one of eight subcategories in our sample. Nineteen patients yielded 76 codes in the second category.

(1) Lack of support means that patients felt inadequately supported by their therapist, for instance because their family had not been integrated in the therapy, or because the therapist ended the therapy when the patient refused to agree to pharmaceutical treatment.

(2) The subcategory *lack of empathy* describes therapists who misunderstood their patients, who did not recognise or validate their problems, and who had failed to respond empathetically to them.

(3) Lack of acceptance/appreciation refers to patients feeling unappreciated or accepted as a person.

> "And what bothered me a lot was that she only defined me by my compulsions, […] every behaviour was marked as compulsive, […] sometimes I got the impression that I wasn't a person anymore, but just OCD […]." (#018)

(4) In the category *lack of fit („mismatching") between the personalities of the therapist and patient*, patients reported the characteristics or behaviours of the therapist they disliked (e.g., "cocky", "bullheaded", "dominant", "ignorant").

(5) If the therapist seemed generally qualified but unable to cope with that particular patient or the disorder's severity, this was categorised under *therapist seemed unable to cope.*

(6) *Difficult hierarchy between therapist and patient* refers to the patient's feeling inferior to the therapist due to real or perceived hierarchical differences.

(7) The category *lack of transparency* incorporates patients who felt the therapist withheld important information:

> "Because in my opinion, she didn't share insights, […] that she'd gained for herself, with me." (#026)

(8) *Therapist went too slow or too fast* means that the patient preferred a different pace.

> "And also the tempo, the speed. Mine [therapist – author's note] was rather slow." (#026)

Category 3: Reasons for negative effects due to unprofessionally performed therapy. In contrast to the first category, the third category refers to origins of NEP in the context of "unprofessional" performed therapy. A total of 58 codings by 16 patients were made in this category. We identified five subcategories.

(1) *Therapeutic error/s* refers to errors by the therapist within the therapeutic setting and treatment, for example if important problems were not addressed during treatment.

> "I was in treatment because of panic and anxiety disorders […]. And I would have preferred practical approaches, well, not just sitting in the room, but actually going outdoors. At least have a little exposure therapy […]." (#027)

(2) Again, *characteristics of the clinical setting* was identified as one category. However, in this context, perceived chaos in the clinic, busy treatment plans, and lacking support by social workers were reported.

> "Well, I would have preferred a different kind of collaboration. With youth welfare services, social services, and advice on how to take action against my husband's behaviour." (#025)

(3) In case patients were not informed about the process, setting, and contents of the therapy, this was characterised as *inaccurate patient information*.

(4) *Therapist not qualified* refers to when patients regarded the therapist as unqualified and when they believed the therapists lacked knowledge about psychological phenomena or the appropriate training/schooling:

> "It was just ignorance about this subject. I mean, I kept asking myself, if you really don't know how dissociations work, why would you be pretending to treat it […]. That was […] a bit confusing, for me as a patient. "(#029)

(5) *Wrong diagnosis* encodes incorrectly interpreted findings and patients who felt they were given the wrong diagnosis.

> "And I was given a few nice diagnoses there. For example, Borderline [Personality Disorder – author's note]. That was the only institution that gave me that diagnosis. Well, everybody else I had to deal with later just shook their head about it. […]" (#023)

Category 4: Malpractice and unethical behaviour. Any therapeutic behaviour considered improper and unethical is allocated to the fourth category in which four subcategories were identified. Eleven patients made 34 codings in this category.

(1) If patients felt put down or humiliated by the therapists' comments or behaviours, this was categorised as *perceived degradation/humiliation by the therapist* when such degradation or humiliation occurred in conjunction with the disorder, personal characteristics, or patients' achievements.

> "Making little of my problems, or ironic comments, rather the therapist satisfying their curiosity […] instead of genuinely responding to me […] For example, every time […] I wanted to talk about my main topic I was interrupted at the start by cheeky comments. That meant it was over for me." (#026)

(2) Under *misuse of power of the therapeutic position*, patients reported the abuse of the therapeutic position, i.e., urging patients to take medication even though they refused, or ordering their compulsory hospitalisation.

(3) *Sexual abuse* means that the patient felt sexually abused by their therapists in any way.

> Interviewer: "[You mentioned that your therapist– author's note] tried to sexually abuse you by inviting you to go to the pool together […] did the acts happen there?"
>
> Patient: "Yes. We were in the public pool and then in the back of his practice, when we were suddenly alone."
>
> Interviewer: "And this is where the abuse happened?"
>
> Patient: "Mmh" (affirmative)
>
> "He always said it was part of the therapy" (#024)

(4) *Profit-orientation at the patient's expense* was categorised when the therapist was perceived as mainly wanting to profit financially from the treatment.

Discussion

This study is the first to systematically evaluate the types and origins of NEP with a mixed-methods design combining qualitative and quantitative analyses. By interviewing former psychotherapy patients, we found that NEP occurred in different areas of life grouped into 15 categories. Patients attributed these effects to different origins that could be classified in four main categories with several subcategories. Two of the main categories are consistent with those in Hoffmann et al.'s model (2008); whereas the other two had to be modified.

The fact that NEP occurred in 15 different categories underlines that they are a rather broad construct and go beyond therapeutic malpractice or worsening symptoms (e.g. Ladwig et al., 2014; Linden, 2013; Nestoriuc, 2015). Eleven of the 15 categories of NEP found in the current sample conformed to the categories of Ladwig et al. (2014). In addition, four new categories were developed, depicting *negative change in personality*, *difficulty trusting others*, *fragile self-concept*, and *lack of complacency*. *Negative change in personality* and *difficulty trusting others* are categories already postulated as revealing NEP (Hoffmann et al., 2008). *Fragile self-concept* and *lack of complacency* have been reported by patients who named depression or eating disorders as their reason for treatment. The related constructs low self-esteem and low self-worth are symptoms of depression (Dilling & Freyberger, 2014) and are very common among individuals with eating disorders (Fairburn, 2012). Hence, in our study, the NEP related to self-concept and complacency might also be closely associated with low self-esteem and thereby actually or at least partly encompass symptom deterioration.

The most frequently named origins for NEP stem from the category *reasons for negative effects of an appropriate therapy*. This category refers to *lege artis* therapies, where the patient perceived the treatment to be adequately carried out by the therapist.

The same applies to the category *problems in the therapeutic relationship*, associated with the second highest number of reported origins; implying that NEP cannot be attributed to the therapist or therapeutic mistakes per se but other factors outside the therapeutic dyad are relevant as well. This phenomenon is observed even within the category *reasons for negative effects due to unprofessionally performed therapy*. Here, aside from the therapist's misconduct, patients also describe shortcomings in the general context of the treatment facility. Especially in inpatient settings, the current health care system demands speedy diagnoses and prompt treatment starts due to tight schedules, which, in some cases, leave limited space for accurate diagnostics, health education, shared decision-making, and a detailed planning for the right interventions. Hence, therapy regarded as unprofessional might at least in part be attributable to societal characteristics and are thereby difficult for therapists to prevent. It is therefore much more important that therapists develop coping strategies for such circumstances with their patients.

About half of the patients reported NEP due to unprofessional and even unethical behaviour by their therapist, referred to as MUB (see definition above). This is in line with our assumption that MUB can actually lead to further NEP. The most frequent complaints were that patients felt humiliated by their therapists or that their psychotherapist misused his or her position of power. While it may seem superfluous to emphasise that therapists adhere to basic ethical principles, our findings show that this is not always the case among practising psychotherapists. However, there could be differences in how these unprofessional behaviours between therapist and patient are perceived. What is perceived as a deep violation of patients' trust might have been intended as constructive criticism on the therapist's part – reflecting a deeply dysfunctional relationship between the two. Further research needs to closely look at

these troublesome interactions between therapists and patients to better understand how they develop and how they can be better handled by therapists and patients alike.

Comparing our categories to those of Hoffmann et al. (2008), we found that two coincide - *reasons for negative effects due to unprofessionally performed therapy* and *malpractice and unethical behaviour*. The category *reasons for negative effects of an appropriate therapy* was broader than Hoffmann's original. Ours integrates origins directly linked to the therapeutic dyad as well as external factors relating to society, the health care system, and clinical setting. Likewise, our category *problems in the therapeutic relationship* represents a broader version of Hoffmann's category *lack of fit („mismatching") between the personalities of the therapist and patient*. The decision for this was because the origins reported by our patients went beyond a perceived mismatching between them and the therapist. In addition, it entails general disruptions in the therapeutic relationship which might be due to the perceived absence of therapeutic base variables such as empathy and support.

Our findings suggest that there are multiple origins for the occurrence of NEP, and that their development is quite complex and should therefore be given particular consideration during the therapeutic process. The fact that they also occur within *lege artis* therapies suggests that they are part of the psychotherapeutic treatment and are not per se caused by therapeutic mistakes or MUB; a frequent assumption that may lead to the fear of litigation and biased, overly cautious, or reluctant reactions to the topic of NEP (Linden, 2013; Sachs, 1983). This new knowledge may be used to make it easier to talk about NEP within the profession and sensitise professionals to these effects. Hence, coping strategies can be developed together with the patient when or even before NEP arise. Communicating the possibility of NEP may also help to destigmatise the therapeutic experience and help patients and therapists to view such factors as

nothing unusual. Discussing potential NEP within treatment may enhance a patient's experience of a collaborative health partnership with their therapist and shift their focus towards managing these unwanted effects rather than avoiding them. Given how sensitive the topic of NEP is, it would make sense for therapists to actively initiate conversations regarding possible NEP rather than merely being receptive to patients' questions or concerns.

Our results should be considered in light of the following limitations. First, while the two category systems for NEP and their origins reveal promising validity within the collected sample, more thorough validation in representative samples is warranted. We specifically interviewed a sample of patients that experienced quite a number of NEP during their psychotherapy. Due to self-serving bias, patients might be more likely to attribute NEP to their therapists or other external factors rather than to factors concerning themselves. In addition, the time between the end of the therapy and study participation varied between patients, and memory biases cannot be ruled out. Second, this study was based purely on the patients' perspectives. It would be interesting to replicate such interviews in a therapist sample. Finally, we note that it was not always possible to distinctly separate NEP and their perceived origins. Thus, a therapeutic relationship perceived as suboptimal can either be the result of perceived MUB or cause possible future NEP themselves. Distinguishing NEP and their origins can be particularly difficult within the categories *problems in the therapeutic relationship* and *malpractice and unethical behaviour*. While creating the coding agenda, we discussed these cases thoroughly and decided on each case individually as to whether patients were describing an origin or an effect.

The current study helps us better understand how and under what circumstances patients experience NEP. Most importantly, we documented a significant number of NEP not

perceived to be caused by therapeutic malpractice or mistakes but that occurred during therapies perceived as otherwise completely adequate. This supports the idea that some NEP must be regarded as a natural, inherent part of the therapeutic process. Moreover, some NEP could result from general shortcomings within the health care system. Especially regarding those effects, coping strategies can be developed to help patients handle them accordingly. Moreover, clinical trials in psychotherapy should be planned to include the systematic assessment of NEP, to enable the benefit-cost ratios of interventions to be adequately assessed. In light of the results, further steps can be undertaken by practitioners and researchers to reduce the potential NEP to a minimum and to raise awareness both within our profession and in patients and the public.

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Table 1. Characteristics of study participants

Variables		n	%
Gender	female	18	75%
Age	21-30 years	8	33.3%
	31-40 years	3	12.5%
	41-50 years	8	33.3%
	51-60 years	5	20.9%
Marital status	single	9	37.5%
	attached	2	12.5%
	married	9	37.5%
	divorced	3	12.5%
Education	secondary general school	1	4.2%
	intermediate secondary school	7	29.2%
	A-level	7	33.3%
	university degree	7	33.3%
Occupation	unemployed	1	4.2%
	employed	12	50%
	pupil/student	5	20.8%
	retired	6	25%
Setting	outpatient	14	58.3%
	inpatient	10	41.7%
Therapy school	psychoanalysis	8	33.3%
	behavioural therapy	4	16.7%
	psychodynamic Therapy	4	16.7%
	other	3	12.5%
	"I don't know"	5	20.8%
Therapy duration	1-5 sessions	2	8.3%
	6-25 sessions	4	16.7%
	26-119 sessions	11	45.8%
	120-300 sessions	5	20.9%
	>300 sessions	2	8.3%

Table 2. Self-reported reasons for seeking psychological treatment referred to in the interview

Patient ID	**"Why did you seek psychotherapy?"**
#006	depression
#009	depression, suicidal thoughts
#014	depression, retraumatisation
#015	depression, anxiety, abuse
#016	depression, partnership and family problems
#021	depression
#008	general anxiety disorder
#004	panic attacks
#010	agoraphobia, compulsive acts, obsessional thoughts
#018	agoraphobia, panic disorder
#002	anxiety and panic disorder, PTSD, ongoing personality changes, dissociation, depersonalisation
#013	PTSD
#017	PTSD
#023	PTSD, dissociative disorder
#001	dissociative disorder
#003	eating disorder
#005	bulimia nervosa, self-harm
#011	bulimia nervosa
#007	obsessive compulsive disorder
#012	multiple personality disorder, suicide attempt
#019	alcohol dependence
#020	chronic fatigue syndrom
#022	chronic fatigue syndrom
#024	general overload and stress

Note. Reasons are clustered according to depression, anxiety disorders, PTSD, eating disorders, and others

Table 3. Examples for the most commonly reported and for the novel, inductively-derived categories of negative effects of psychotherapy

	Negative effect	**Example quotations**
Most commonly reported categories	Problems in the therapeutic relationship	"There was basically no support. We just made small talk […] and after ten sessions there comes a point where things don't get any better." (#016) "Just antipathy, plain antipathy. I'd say I sensed a total lack of sympathy." (#019) "The therapists have everything so firmly in control that you're too afraid to say anything at all, otherwise you feel like you'll be thrown out of the hospital." (#029)
	Existing symptoms	"Well, it would have been nice, if my symptoms had changed, I mean if they had improved."(#007) "It just did not do me any good. Because things just got worse for me." (#009)
	New symptoms	"Certain composure, it's like I lost almost all of it." (#018) "All of a sudden I felt very dizzy." (#022)
Inductively created categories	Fragile self-concept	"Yes, there was a time during the therapy when I was quite unstable, totally unstable and quite uncertain about myself as a person. Everything I pictured about myself went out the window. It was extremely destabilising at the time." (#017)
	Difficulty trusting others	"I started to trust people a lot less. Now I'm less inclined to talk about my problems with others. Yes, generally you could say that I've become even more withdrawn." (#027)
	Lack of complacency	"Interviewer: "Was there a subject that was important to you but didn't change during treatment?" Patient: "Yes, maybe some kind of inner peace. Something like that. More complacency. It's not like that at all." (#010)
	Negative	"I've always been very meticulous, fastidious and exact. And I was able to let that go. After the first therapy I started

	change in personality	living in the moment and taking each day a time. But that just completely changed again with the last treatment. I lost that again." (#018)

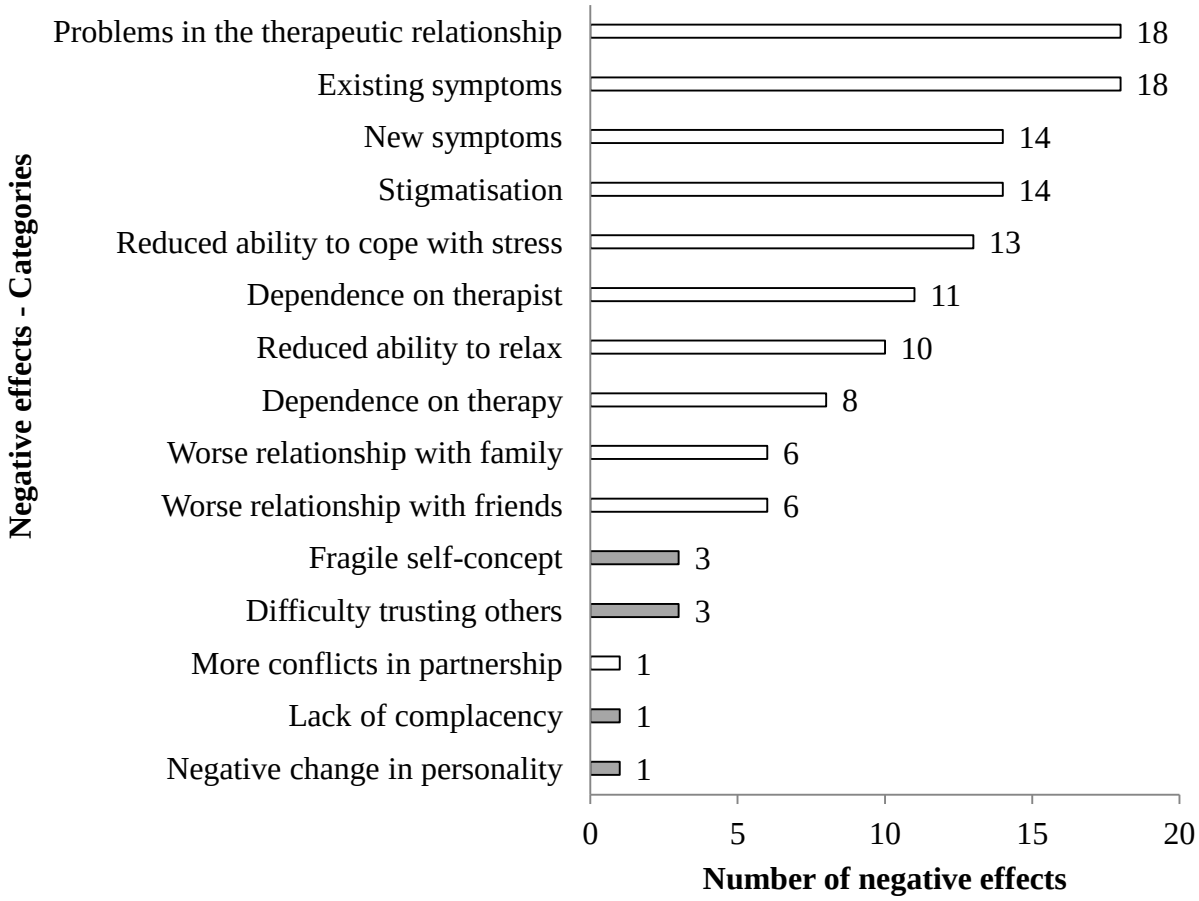
Note. Patient ID in brackets

Table 4. List of categories and subcategories for patients' attributions regarding the origins of perceived negative effects

Category	k	n
1. Reasons for negative effects of an appropriate therapy	**131**	**24**
Characteristics of patients' environment	37	21
Characteristics of the patient	32	17
Characteristics of the therapeutic setting	14	9
Dependency on therapist or therapy	12	8
Not the right therapy/technique	11	7
Therapy as a process that reveals and changes things	11	7
Lack of success and deterioration	8	7
Characteristics of the clinical setting	1	1
2. Problems in the therapeutic relationship	**76**	**19**
Lack of support	19	13
Lack of empathy	15	9
Lack of acceptance/appreciation	13	11
Lack of fit („mismatching") between the personalities of the therapist and patient	12	8
Therapist seemed unable to cope	8	7
Difficult hierarchy between therapist and patient	3	2
Lack of transparency	3	2
Therapist was too slow or too fast	3	2
3. Reasons for negative effects due to unprofessionally performed therapy	**58**	**16**
Therapeutic error/s	24	11
Characteristics of the clinical setting	13	6
Inaccurate patient information	8	6
Therapist not qualified	7	5
Wrong diagnosis	5	4
4. Malpractice and unethical behaviour	**34**	**11**
Perceived degradation/humiliation by the therapist	15	7
Misuse of power of the therapeutic position	15	7
Sexual abuse	3	1
Profit-orientation at the patient's expense	1	1

Notes. k= frequency of codings of each origin, n = number of patients who reported origin.

Figure 1. Categories for the 127 negative effects of psychotherapy reported within the sample - deductive (displayed in white) as well as inductive categories (displayed in grey) derived from the material are displayed



A.4 Studie 4

Different treatment settings reveal various rates of negative effects of psychotherapy: Exemplifying the need to evaluate negative effects of psychotherapy by comparing a psychiatric to a psychosomatic hospital

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Abstract

Studies examining the rates of negative effects of psychotherapy are rare and the reported rates differ widely. To be able to calculate adequate benefit-cost ratios in conjunction with different samples and settings, we need a deeper understanding of these effects. We therefore investigated whether different treatment settings would reveal varying rates and kinds of negative effects by recruiting patients from a psychiatric (n=93) and a psychosomatic rehabilitation (n=63) hospital. Negative effects of psychotherapy were assessed with the Inventory for the Assessment of Negative Effects of Psychotherapy post-treatment. Patients from the psychiatric hospital reported an average 1.41 negative effects, with 58.7% reporting at least one negative effect. Those from the psychosomatic hospital reported 0.76 negative effects on average, with 45.2% of patients reporting at least one negative effect. The differences between these samples are significant. The two samples' most frequently reported types of negative effects correspond. Our study highlights the need to examine the negative effects of psychotherapy in different settings and samples to better evaluate the benefit-cost ratios of treatments for different patient groups. It also shows that we need guidelines for assessing and reporting negative effects.

Keywords: side effects, malpractice

1. Introduction

After having been neglected for decades (Duggan et al., 2014), the negative effects of psychotherapy are now attracting more attention in psychotherapy research (Barlow, 2010; Lilienfeld, 2007; Rozental et al., 2014) and instruments for their assessment have been developed (Ladwig et al., 2014; Linden, 2013; Moritz et al., 2015). Nevertheless, studies on the incidence of negative effects are still rare and factors facilitating their development are not identified yet. Moreover, prevalence rates differ according to how they have been methodically assessed, how negative effects are defined, and according to the setting in or sample from which data are collected (Crawford et al., 2016; Ladwig et al., 2014). Hence, in order to be able to evaluate adequate benefit-cost ratios, to help prevent such effects, and to develop coping strategies for them in the long run, more studies investigating the occurrence of and influencing factors for negative effects are needed.

Awareness of the possibility that psychotherapy can cause harm has long been acknowledged (Barlow, 2010), and as early as the 1960s Bergin was describing the "deterioration effect", stating that patients might become worse through psychotherapy (Bergin, 1966). Since then, other researchers have investigated deterioration and non-response (e.g., Jacobi et al., 2011; Kraus et al., 2011). However, it becomes more and more evident that negative effects of psychotherapy go beyond mere symptom deterioration, and that they can affect different areas of patients' lives (Ladwig et al., 2014; Moritz et al., 2015). Accordingly, there are several terms to describe psychotherapy's negative effects: unwanted events, adverse treatment reactions, symptom deterioration, side effects, damage, malpractice, etc. (Hoffmann et al., 2008; Linden, 2013; Mohr and Francisco, 1995). In our article, we define negative effects of psychotherapy (NEP) as all changes that the patient experiences as being negative, that occur during or after psychotherapy, and that the patient attributes to the psychotherapy. NEP that occur after *lege artis* therapies can be referred to as side effects, whereas malpractice and unethical behaviour (MUB) are not associated with *lege artis* therapies (compare Ladwig et al., 2014).

Taking a closer look at the literature with this definition in mind, one notices that few studies have investigated NEP that go beyond symptom deterioration or non-response (e.g., Buckley et al., 1981; Crawford et al., 2016; Ladwig et al., 2014; Moritz et al., 2015), and that the rates of reported negative effects differ among studies. In a national survey in England and Wales, 5.2% of psychotherapy

patients reported having experienced lasting bad effects from their psychological treatment (Crawford et al., 2016). Ladwig et al. examined NEP in different areas of patients' lives in a German online sample of previous psychotherapy patients, of whom 93.8% reported having experienced at least one NEP. The study by Buckley et al. (1981) examined psychotherapists who had been in treatment themselves; 21% of them reported negative effects from their psychotherapy. The large variations in these frequencies might be due to differences in definition (e.g., lasting bad effects versus NEP in different areas of patients' lives), samples, assessment methods, and treatment modalities. Ladwig et al. (2014) for instance found that patients who had been treated in a hospital reported more NEP than those who underwent outpatient treatment. These differences between samples illustrate that more studies on NEP are needed to gain a deeper understanding of these effects and to evaluate adequate benefit-cost ratios of treatments for different samples. So far, we have only been able to compare the NEP rates between samples from different studies. As already mentioned, this is associated with several sources of bias. An important next step would thus be to examine whether reported NEP also differ between treatments or treatment settings when the assessment method and definition of NEP are identical between the samples. One could thus also examine whether instruments for assessing NEP are sensitive in detecting differences. Germany offers particular opportunities to address such issues, since in addition to psychiatric hospitals, many patients undergo therapy in psychosomatic rehabilitation hospitals (Linden, 2014). The major difference between these two treatment modalities is that psychiatric hospitals focus more on pharmacological treatments, whereas psychosomatic rehabilitation hospitals focus more on psychotherapeutic therapies, although both kinds of treatments are applied in these two hospital settings, the diagnoses are comparable, and treatments tend to be very similar (Beutel and Subic-Wrana, 2010).

One might also question what factors influence the experience of NEP other than different treatment settings. From psychotherapy research we know that patients' positive expectations regarding treatment are associated with more positive therapy outcome (Constantino et al., 2011). But does that also mean that positive treatment expectations are associated with fewer NEP? Ladwig et al. found that if patients' therapy expectations had not been met, they reported more NEP. The fulfilment

of those expectations was assessed post-treatment. Therefore, it would be interesting to examine whether patients' pre-treatment expectations regarding the therapy influence the occurrence of NEP.

In this study we aimed to investigate whether different treatment settings reveal varying rates and kinds of negative effects. To do so we examined patients from a psychosomatic rehabilitation hospital and those from a psychiatric hospital. We also investigated whether patients' pre-treatment expectations exert an additional influence on NEP.

2. Methods

2.1. Participants and setting

Our study participants were recruited in two different hospitals – a psychosomatic rehabilitation hospital and a psychiatric hospital – in Germany in 2015 and 2016. The treatment in the psychosomatic rehabilitation hospital was mainly cognitive-behavioural; in the psychiatric hospital it was partly cognitive-behavioural and partly psychodynamic. In the psychiatric hospital, we recruited only patients from wards that worked psychotherapeutically. In contrast to the psychiatric hospital, participants with acute psychosis, acute suicidal tendencies, and substance abuse syndrome were not treated in the psychosomatic rehabilitation hospital.

2.2. Measures

Negative effects. The Inventory for the Assessment of Negative Effects of Psychotherapy (INEP) served as our primary outcome measure (Ladwig et al., 2014). The INEP assesses negative as well as positive effects in different areas of patients' lives (e.g., friends, family, stigmatisation, etc.) that occurred during or after the patient's psychotherapy. For each positively answered item, patients have to indicate whether an effect can be attributed to the treatment, to other circumstances, or to both. The first six items are bivariate and assess negative and positive effects on a 7-point-Likert scale. Items 7 to 21 only assess negative effects on a 4-point-Likert scale. Zero indicates "no change" in both cases. Hence, the intensity of NEP per item ranges from one to three. Items 16 to 21 assess MUB and are not summed up in the INEP's total score as they are supposed to be evaluated individually. For those items, patients can provide further explanations in an open format. An intensity score for NEP can be calculated, as can a simple score of negative effects. We calculated a simple NEP score for this study

by adding all the negative effects that had been rated as therapy-related without taking each effect's intensity into account. Accordingly, between 0 and 15 negative effects and between 0 and 6 MUB could be reported.

Expectations. Expectations regarding treatment outcome were assessed with the Patient Questionnaire on Therapy Expectation and Evaluation (PATHEV) (Schulte, 2005). The PATHEV consists of three subscales: Hope of Improvement (e.g., "I believe my problems can finally be solved."), Suitability (e.g., "I've found the right therapy."), and Fear of Change (e.g., "From time to time I worry about all the things that will change once my problems have vanished."). The subscales reveal an internal consistency between $\alpha = .73$ and $\alpha = .89$ (Schulte, 2005).

2.3. Procedure

During the first week of their treatment in the hospital, participants were handed out the pre-treatment questionnaire by the study personnel. Prior to filling in the questionnaire, written informed consent was obtained from all participants. Post-questionnaires were handed out to the patients during the last week of their hospital stay. In the psychosomatic hospital, participants filled in the questionnaires at fixed assessment points together with other patients and in the presence of a study staff member. Patients from the psychiatric hospital answered the questionnaires during their first and their last week and handed it back to the study personnel. Pre-treatment questionnaires contained the PATHEV and questions about previous psychotherapies including the INEP. Post-treatment questionnaires contained the INEP with the instruction to refer to the current treatment in the hospital when answering the questions, the Helping Alliance Questionnaire (HAQ) (Bassler et al., 1995) which is used to evaluate the therapeutic relationship, and questions about the treatment. Demographic variables, pre- and post-treatment scores from the Beck Depression Inventory (BDI-II) (Hautzinger, 1995) for assessing depressive symptoms, and diagnoses were gathered from each hospital's documentation system.

2.4. Statistical analyses

Statistical analyses were conducted with IBM SPSS Statistics 21.0. Differences between groups were investigated using t-tests for independent samples or χ^2-tests. To test for associations between treatment expectations and NEP, bivariate correlations for the PATHEV subscales with NEP were

investigated. Next, a hierarchical linear regression analysis was done to test whether pre-treatment expectations predict treatment outcome. Missing data in the INEP were regarded as if no NEP was present or as if the NEP was not attributable to the psychotherapeutic treatment. To overcome the problem of missing data in the PATHEV, we calculated each participant's mean score on the PATHEV subscales. Participants with missing data in any of the other predictor variables included in the regression were excluded from regression analyses. Sample characteristics were analysed via frequency analyses. Outliers were investigated using boxplots. Since negative effects of psychotherapy are not normally distributed and there were extreme values, values exceeding three interquartile ranges from the upper quartile of the group median were excluded from data analyses. This applied to four study patients.

3. Results

3.1. Sample characteristics

All in all, 203 participants from the two clinics were willing to participate in the study and filled in the pre-questionnaire. Of these, 160 (79%) also filled in the post-questionnaire. For a detailed flow-chart, see Figure 1. Participants from the psychosomatic rehabilitation hospital were significantly older and more often in a relationship or married. Patients from the psychiatric hospital had higher pre-treatment depression scores as measured by BDI. However, post-treatment BDI scores did not differ between patients from the two clinics. More of the psychiatric patients reported having dropped out of a previous psychotherapy than patients from the psychosomatic hospital (see Table 1). We observed no differences between the samples regarding sex, days spent in the hospital, number of mental or behavioural diagnoses according to ICD-10, prior experiences with psychotherapy, satisfaction with the therapeutic alliance, the demands the treatment made of them, and pre-treatment expectations.

3.2. Frequency of negative effects of psychotherapy

Participants in the psychiatric hospital reported an average 1.41 NEP, with 58.7% reporting at least one NEP. An average 0.76 NEP were reported in the psychosomatic rehabilitation hospital, with 45.2% of patients reporting at least one NEP (Figure 1). The difference in reported NEP between the two hospitals is significant ($t(94.54) = -2.76$, $p = .007$). When analysing NEP on single-item basis

(Table 2), it becomes evident that the most frequently reported NEP in both hospitals was that the patient had experienced more downs during or just before the end of the therapy (psychosomatic sample: 31.2%, psychiatric sample: 30.2%). In addition, the items addressing difficulty making important decisions without the therapist (psychosomatic sample: 9.7%, psychiatric sample: 25.4%) and being concerned that colleagues or friends might find out about the therapy (psychosomatic sample: 10.8%, psychiatric sample: 19.0%) are the most frequently mentioned NEP. Although the top three reported NEP between the two hospitals are the same, the frequency of how often NEP were reported differed between the two hospitals' patient groups. The sample from the psychiatric hospital revealed much higher ratings regarding the items stigmatisation, financial worries, problems with insurers, feeling addicted to the therapist, and having difficulty making important decisions alone in particular. In terms of MUB, patients reported most often that they felt hurt by what the therapist told them (psychosomatic sample: 11.9%, psychiatric sample: 12.7%). Very few participants reported having felt personally ridiculed by their therapist (psychosomatic hospital: 3.3%, psychiatric hospital 7.9%) and that they had been forced to do things they did not want to do (psychosomatic sample: 5.4%, psychiatric sample: 3.2%). One patient from the psychosomatic sample reported having been physically attacked by the therapist, and another reported that the therapist broke confidentiality. None of the patients felt sexually molested by their therapist.

3.3. Predictors for negative effects of psychotherapy

From the PATHEV subscales, only Hope of Improvement yielded a significant correlation with NEP ($r_{Pearson}$ = -.17, p = .033). We detected no association with NEP in the subscales Suitability ($r_{Pearson}$ = -.15, p = .063) and Fear of Change ($r_{Pearson}$ = .06, p = .47). Therefore, only Hope of Improvement was entered in the regression model in the third step.

In the first step, age, gender, and clinical setting were entered in the regression model. From these variables, only the clinical setting was a significant predictor of NEP (β = 0.24, p = .004) in the way that patients from the psychiatric hospital were more likely to report NEP. The pre-treatment depressive symptoms entered in the second step could not explain any additional variance. However, the third step of our regression model showed that expectations (hope of improvement) were an additional significant predictor for the experience of NEP (β = -0.17, p = .033), meaning that patients

who are more hopeful of improvement experience fewer NEP. The overall model explains 11.1% of the variation in reported NEP (see Table 3). Since the assumption of normality was violated, the regression was also carried out using bootstrap; results were the same.

4. Discussion

By comparing patients from a psychosomatic rehabilitation hospital to those in a psychiatric hospital, we demonstrated that different treatment settings reveal varying rates of reported negative effects. Patients from both hospitals experienced a substantial number of NEP, with more NEP reported in the sample from the psychiatric hospital. The most frequently reported NEP corresponded between patients in the two hospitals. Apart from the clinical setting, expectations in the form of hope of improvement predicted the number of reported NEP, meaning that patients who are less optimistic towards the treatment report more NEP.

Our study revealed that rates of NEP differ between patient groups from different hospitals although their treatments are usually very similar. On the one hand, this finding shows that the INEP is sensitive in detecting differences. On the other hand, it also underlines the necessity to examine NEP in different samples and settings to include these differences when calculating the benefit-cost ratios of treatments. The differences in reported NEP between different samples become even more obvious when comparing our study's results to those of other studies (Crawford et al., 2016; Ladwig et al., 2014; Moritz et al., 2015). Whereas Crawford et al.'s study numbers are substantially lower (with 5.2% reporting lasting bad effects), reported numbers in other studies are much higher, with up to 93% of patients reporting at least one NEP (Ladwig et al., 2014; Moritz et al., 2015). Although the numbers of reported NEP in our study differ between the two hospitals, they are more similar to each other than to the other studies' numbers. This speaks for the fact that the assessment method, assessment point, and NEP definition make a difference in measured NEP. In our study, we did not carry out a follow-up assessment, meaning that the effects that only occurred after the hospital stay were not accounted for. Furthermore, it is possible that, although we assured our patients that the assessment is anonymous and their therapist would know nothing about their answers, this study's patients did not disclose as much as those in Ladwig et al.'s online sample. On the other hand, it is possible that especially those

patients who had experienced NEP in a previous treatment were interested in answering the online questionnaire. That different studies yield different numbers of side effects is a phenomenon also known from drug trials (Rief et al., 2006). There is evidence that detailed assessments with symptom-lists result in more side-effect reporting than open-ended questions (Rief et al., 2009). The described findings imply that guidelines are needed for assessing and reporting NEP in clinical trials. Without them, benefit-cost ratios of treatments cannot be adequately evaluated, since lower numbers of reported NEP in one treatment as compared to another might only be due to a different means of assessment and not because fewer NEP actually occurred.

Nevertheless, although differences between our study and others might be explained by differences in assessment methods or NEP definitions, the differences between our study's two samples cannot be attributed to such circumstances. What might have caused the differences between the samples from the two hospitals? One reason might be that patients from the psychiatric hospital were more severely disturbed, as revealed in the higher pre-treatment depression scores. This higher symptom severity might have led to more changes during treatment, including negative changes. Nevertheless, in the regression, the depressive symptoms failed to predict NEP, which argues against this assumption. On the other hand, one can imagine another link between higher depression scores and higher numbers of NEP in the psychiatric sample, particularly when scrutinising on a single-item basis. It becomes evident that the differences between the hospitals were especially pronounced in the item addressing problems in making important decisions without the therapist. Indecision or indecisiveness is also a sign of depression (Dilling and Freyberger, 2014). Another of the items on which differences between the hospitals were particularly pronounced was feeling addicted to the therapist, which might be closely linked to the aforementioned item.

Interestingly, the NEP that were most frequently reported corresponded between the two hospitals and resemble those in Ladwig et al.'s study (Ladwig et al., 2014). Knowing that patients suffer from the same NEP across samples is an important finding, since therapists can therefore pay particular attention to the occurrence of these NEP, and develop coping strategies with the patients accordingly. The items addressing MUB were also answered similarly by patients from both hospitals and

correspond to Ladwig et al.'s study. Apart from that, not many MUB were reported in the current study - a promising result.

Patients who have more hope of improvement regarding the treatment experienced fewer NEP, meaning that a more optimistic attitude towards therapy might be a protecting factor when it comes to NEP or to put it the other way round, being less optimistic might trigger more NEP. This result is in line with studies showing that positive treatment expectations lead to a more positive treatment outcome (Rheker et al., 2015). Taken together it means that enhancing a patient's expectations towards the therapy at treatment start might lead to more positive outcomes in terms of main outcome and NEP. However, there is evidence that wanted and unwanted effects of a treatment correlate negatively (Moritz et al., 2015), meaning that if reported NEP are confounded with a treatment's main outcome, and since expectations predict main outcome, they might thereby also predict NEP. The association between NEP, wanted treatment effects, and expectations should be more thoroughly investigated in future studies.

This leads to the first limitation of our study: We did not assess patients' main treatment outcome. In light of the finding by Moritz et al., it would have been interesting to examine whether and how reported NEP are associated with symptom improvement. In addition, our study is limited by the fact that we did not do any follow-up assessments, but rather measured NEP immediately at the end of the hospital stay. Due to the hospitals' data protection policies, we could not contact the patients after the end of their hospital stay. We therefore had to modify two items (13 and 15) on the INEP that usually target the evaluation of NEP both during and after the end of treatment in the long run. In our study we only asked for the effects during or just before the end of the treatment. Another limitation are the differences how NEP were assessed between the two hospitals (being given an appointment for the assessment, versus filling in the questionnaire alone). Participants could have answered differently in the presence of study personnel.

Despite these limitations, this study makes an important contribution to the few existing empirical studies on NEP, and it contains implications for future research: the fact that the incidence of reported NEP differs between the hospitals and in comparison to other studies shows the importance of investigating NEP in different settings and via different studies applying similar methods. It also

shows that we need guidelines for assessing NEP, particularly when it comes to clinical trials. The high numbers of reported NEP lead to the question whether NEP should be regarded as a necessary evil or whether they are preventable - a key question that future investigations should address .

Conflict of interest

The authors have no conflict of interest to declare.

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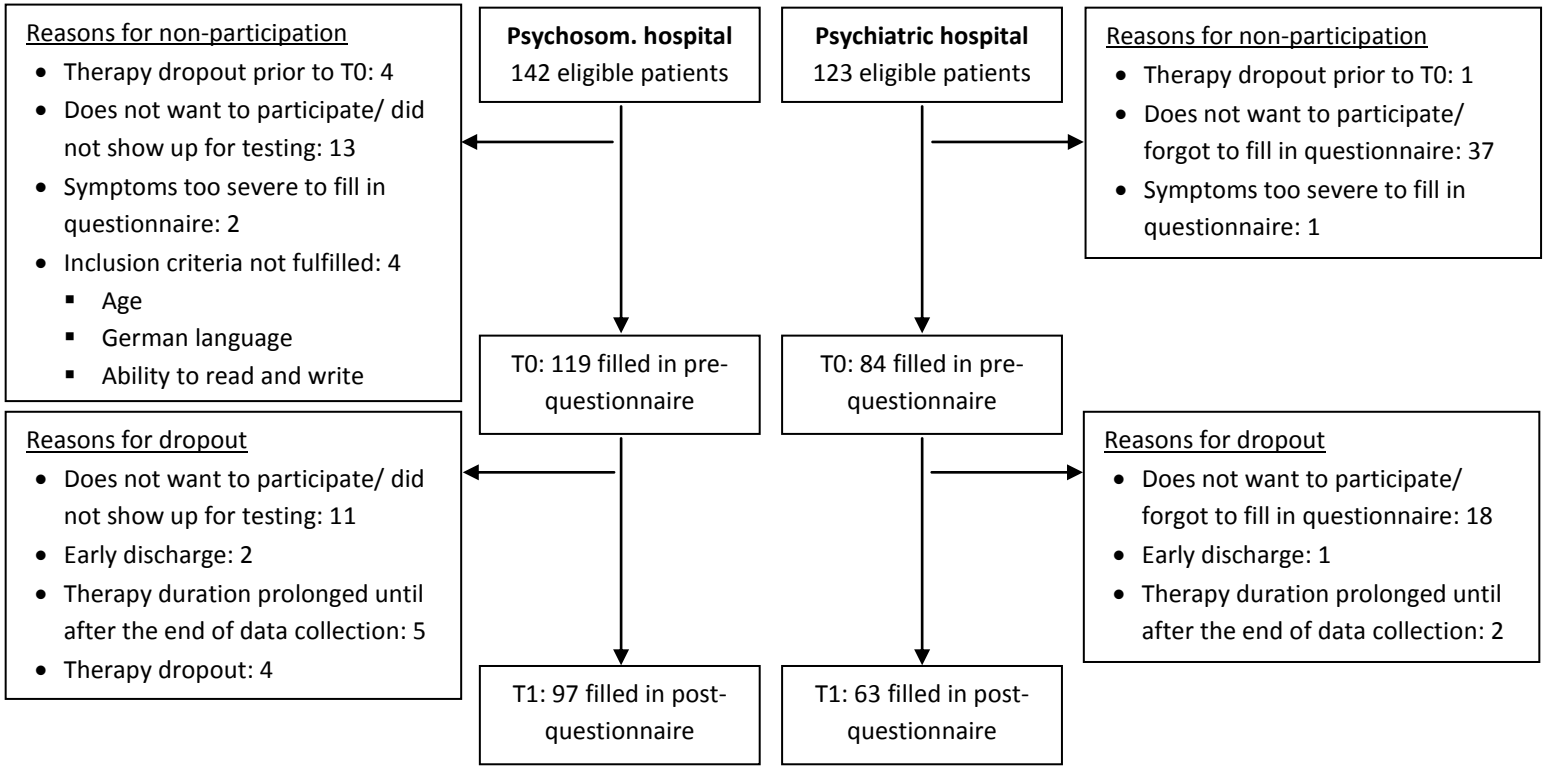

Fig 1 Flow of participants

Table 1 Sample Characteristics

Characteristics	Psychosomatic hospital		Psychiatric hospital		Group differences
	n in analyses		n in analyses		
Age in years, *M (SD)*	93	45.62 (10.73)	63	37.24 (13.61)	$t(111.85) = 4.13$, $p < .001$
Number females, *n (%)*	93	52 (55.9 %)	63	32 (50.8%)	$\chi^2(1) = .40$, $p = .529$
In relationship or married, *n (%)*	93	63 (67.7%)	62	30 (47.6%)	$\chi^2(1) = .581$, $p = .016$
Days spent in current clinic, *M (SD)*	93	36.82 (6.65)	61	34.07 (12.93)	$t(81.07) = 1.54$, $p = .129$
BDI-II score pre-treatment	92	18.09 (8.02)	62	25.76 (11.31)	$t(101.46) = -4.62$, $p < .001$
BDI-II score post-treatment	89	11.58 (10.06)	59	12.19 (10.08)	$t(146) = -0.36$, $p = .722$
Number of ICD-10 F-diagnoses, *M (SD)*	93	2.31 (1.04)	63	2.11 (1.21)	$t(154) = 1.11$, $p = .270$
Prior experience with psychotherapy, *n (%)*	93	64 (68.8%)	62	46 (73.0%)	$\chi^2(1) = 0.52$, $p = .470$
Negative effects in prior therapy, *n (%)*[1]	64	32 (50.0%)	46	25 (54.3%)	$\chi^2(1) = 0.20$, $p = .653$
Dropout from prior therapy, *n (%)*[1]	63	8 (12.5%)	46	16 (34.8%)	$\chi^2(1) = 7.55$, $p = .006$
Demands of the therapy	89		63		$\chi^2(2) = 0.52$, $p = .769$
Treatment was not demanding enough		10 (10.8%)		8 (12.7%)	
Treatment was exactly right		64 (68.8%)		47 (74.6%)	
Treatment was too demanding		15 (16.1%)		8 (12.7%)	
Satisfaction with therapeutic alliance, *M (SD)*	89	28.38 (6.52)	62	29.10 (7.94)	$t(149) = -0.61$, $p = .546$
Pre-treatment expectations, *M (SD)*					
PATHEV Hope of Improvement	92	3.41 (0.78)	63	3.58 (0.79)	$t(153) = -1.36$, $p = .177$
PATHEV Suitability	91	3.75 (0.57)	62	3.55 (0.72)	$t(151) = 1.89$, $p = .061$
PATHEV Fear of Change	92	2.14 (0.92)	63	2.37 (0.91)	$t(153) = -1.51$, $p = .133$

Note: [1] % only for patients with prior psychotherapy experience; PATHEV= Patient Questionnaire on Therapy Expectation and Therapy Evaluation; Hope of Improvement =subscale of the PATHEV; Suitability=subscale of the PATHEV; Fear of Change=subscale of the PATHEV

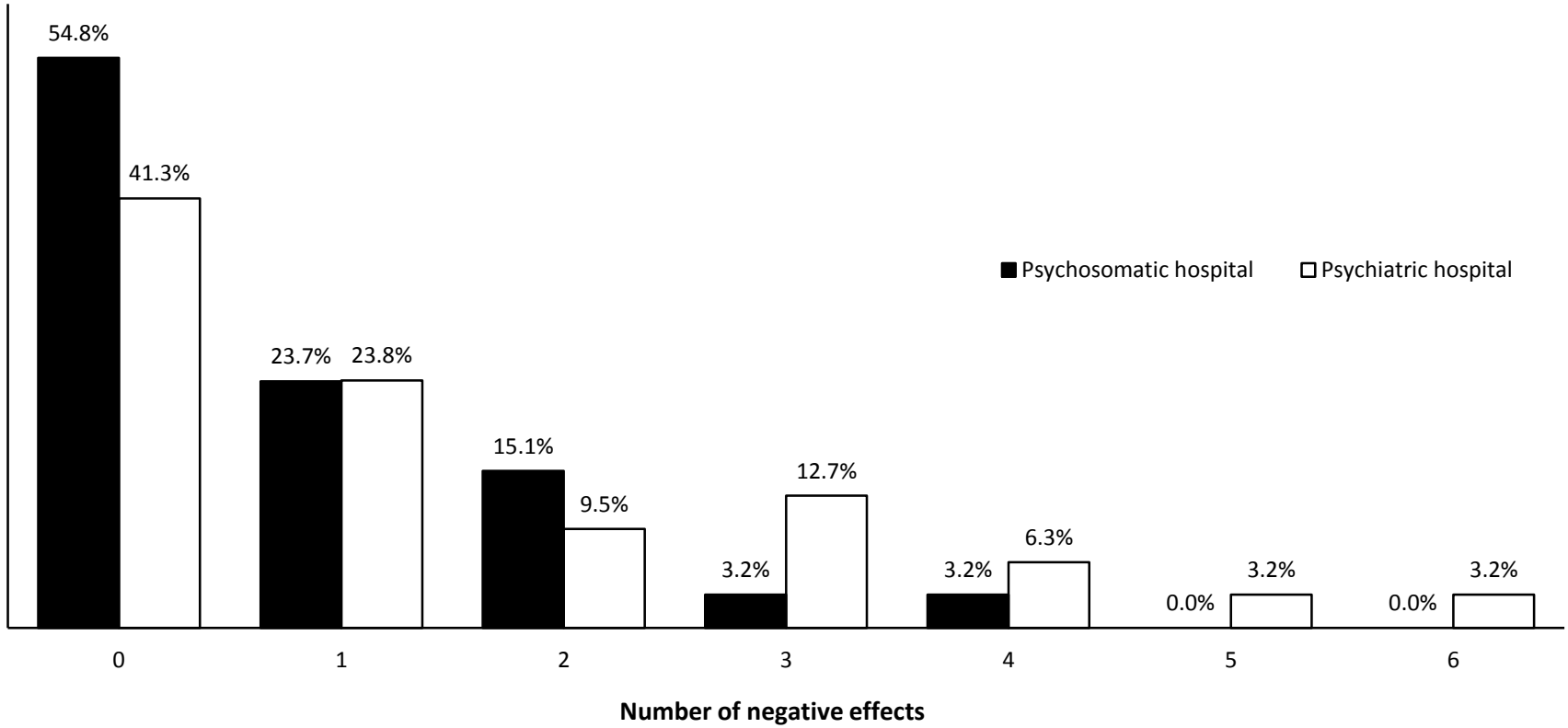

Fig 2 Frequency of negative effects in the two hospitals

Table 2 Frequency of negative effects per item and group

Negative effect of psychotherapy (INEP item)	Psychosomatic hospital (n=93)		Psychiatric hospital (n=63)	
	n	**%**	**n**	**%**
1. I feel worse.	1	1.1	0	0
2. Trusting others comes harder.	2	2.2	1	1.6
3. I am more troubled by my past.	4	4.3	1	1.6
4. My partner and I experience more conflicts.	3	3.2	3	4.8
5. The relationship with my family has worsened.	2	2.2	2	3.2
6. The relationship with my friends has worsened.	0	0	1	1.6
7. I am anxious that my colleagues or friends could find out about my psychotherapy.	10	10.8	12	19.0
8. I have troubles finding insurance or am anxious to apply for new insurance.	1	1.1	7	11.1
9. I have more financial worries than before.	4	4.3	9	14.3
10. I feel addicted to my therapist.	4	4.3	11	17.5
11. I have troubles making important decisions without my therapist.	9	9.7	16	25.4
12. My partner is or has been jealous of my therapist.	0	0	4	6.3
13. Everybody has ups and downs. During or just before the end of my therapy, I have experienced more downs.	29	31.2	19	30.2
14. I have changed for the worse.	2	2.2	3	4.8
15. During or just before the end of my therapy, I suffered from suicidal thoughts or intentions for the first time ever.	0	0	0	0
16. I felt hurt by what the therapist told me.	11	11.9	8	12.7
17. I felt personally ridiculed by my therapist.	3	3.3	5	7.9
18. I felt sexually molested by my therapist.	0	0	0	0
19. My therapist attacked me physically.	1	1.1	0	0
20. My therapist forced me to do things I did not want to do (e.g., confrontations, role plays).	5	5.4	2	3.2
21. My therapist broke confidentiality.	1	1.1	0	0

Note: Only negative effects as assessed by the Inventory for the Assessment of Negative Effects of Psychotherapy (INEP) patients attributed to the treatment or to the treatment and other circumstances are counted as negative effect of psychotherapy

Table 3 Expectation as a predictor of outcome

Step	Predictor	B	SE	β	p	Model R^2	F	p	Change in R^2	Change in F	p
1						.066	3.53	**.017**	.066	3.53	**.017**
	Sex	0.26	0.22	0.10	.244						
	Age	0.002	0.01	0.02	.802						
	Clinical Setting	0.68	0.23	0.24	**.004**						
2						.083	3.35	**.012**	.017	2.69	.103
	Sex	0.32	0.23	0.12	.161						
	Age	0.00	0.01	0.003	.971						
	Clinical Setting	0.51	0.25	0.19	**.043**						
	BDI pre-treatment	0.02	0.01	0.14	.103						
3						.111	3.67	**.004**	.028	4.63	**.033**
	Sex	0.29	0.22	0.11	.194						
	Age	0.002	0.01	0.02	.835						
	Clinical Setting	0.63	0.25	0.23	**.015**						
	BDI pre-treatment	0.01	0.01	0.10	.281						
	PATHEV-Hope of Improvement	-0.30	0.14	-0.17	**.033**						

Note. n=153; dependent variable=negative effects of psychotherapy; SE=standard error; BDI=Beck Depression Inventory II, PATHEV=Patient Questionnaire on Therapy Expectation and Evaluation

B. Lebenslauf

(Der Lebenslauf ist nicht Teil dieser Veröffentlichung.)

C. Eidesstattliche Erklärung

Ich versichere, dass ich meine Dissertation

„Behandlungserwartungen im Kontext pharmakologischer und psychologischer Interventionen – Einfluss auf positive und negative Behandlungsergebnisse“

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

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

Marburg, September 2016 Julia Rheker