INTERNETBASIERTE INTERVENTIONEN ZUR BEHANDLUNG VON DEPRESSIONEN – WER PROFITIERT, WER NICHT? PSYCHOLOGISCHE, SOZIALE UND MOTIVATIONALE FAKTOREN, DIE DEN BEHANDLUNGSERFOLG BEEINFLUSSEN

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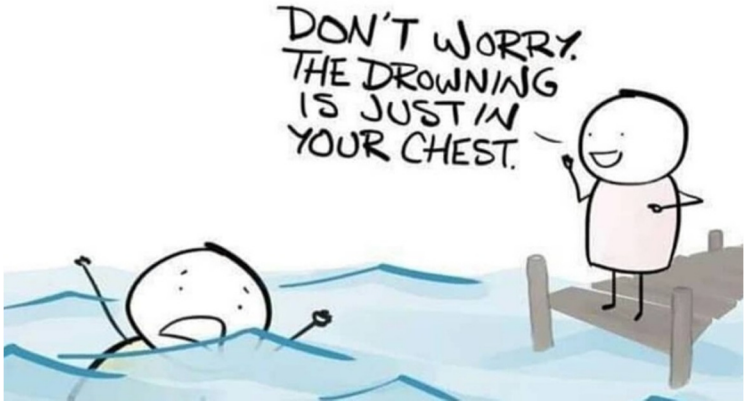

Quelle: Instagram @cbulloch13 #itsokaynottobeokay

Everyone you meet is fighting a battle

you know nothing about.

Be kind.

Always.

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Ich kann noch nicht glauben, dass dieser Tag nun wirklich gekommen ist. Ohne die Unterstützung vieler Menschen hätte ich es nicht bis hierhin geschafft. Nun bin ich glücklich und stolz, allen Widerständen zum Trotz nicht aufgegeben zu haben. Mein Dank gilt allen, die an meiner Seite waren.

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INHALTSVERZEICHNIS

1. Zusammenfassung und Abstract

1.1 Zusammenfassung

Aufgrund der starken Beeinträchtigung der Lebensqualität beim Erleiden von depressiven Symptomen und der hohen Prävalenzraten spielen Depressionen eine gewichtige Rolle im Forschungsfeld der mentalen Gesundheit. Durch eine zunehmende Digitalisierung erscheint es naheliegend, depressive Störungen auch mithilfe internetbasierter Maßnahmen zu behandeln – mit dem Ziel, Betroffenen auf diese Weise neben der traditionellen Psychotherapie weitere Unterstützungsangebote zur Verfügung stellen und zugleich Behandlungsbarrieren überwinden zu können.

Für den effektiven Einsatz internetbasierter Interventionen existiert bereits vielfältige Evidenz – sowohl für Betroffene mit majoren Depressionen als auch für Personen, die subklinische Beschwerden aufweisen. Bisher gibt es allerdings nur begrenzte Erkenntnisse darüber, ob internetbasierte Maßnahmen zur Behandlung von majoren Depressionen auch aktiven Kontrollbedingungen überlegen sind. Die Ergebnisse einer randomisiert-kontrollierten Studie (RCT = randomized controlled trial) zum Vergleich einer internetbasierten Intervention mit reiner Online-Psychoedukation (Studie 1) zeigen, dass dies zutrifft. Darüber hinaus ist die Erkenntnislage für Personen mit subklinischen depressiven Symptomen hinsichtlich ihrer langfristigen Wirksamkeit inkonsistent. Eine Meta-Analyse auf Basis der individuellen Teilnehmerdaten (IPD-MA = individual participant data meta-analysis) zur Evaluation der Wirksamkeit internetbasierter Maßnahmen zur Behandlung von subklinischen depressiven Symptomen (Studie 2) führte zu einer kurz-, mittel- und langfristigen Überlegenheit der Behandlungsgruppe im Vergleich zur Kontrollgruppe. Eine zusätzliche Analyse ergab, dass das Risiko für die Entwicklung einer majoren Depression innerhalb von 12 Monaten in der Interventionsgruppe im Vergleich zur Kontrollgruppe 28 % geringer ist. Für die Implementierung internetbasierter Maßnahmen in die Routineversorgung ist es gegebenenfalls erforderlich, geeignete Maßnahmen zu ergreifen, um mit den Studienergebnissen vergleichbar hohe Effekte bei den Betroffenen zu erreichen.

Die Identifizierung von Faktoren, die den Behandlungserfolg beeinflussen, ist von großem Interesse, um internetbasierte Maßnahmen geeigneten Populationen kosteneffektiv und mit maximalem Nutzen zur Verfügung stellen zu können. Die IPD-MA für Personen mit subklinischen Symptomen (Studie 2) zeigte, dass eine hohe initiale Symptomschwere und höheres Alter zu einer niedrigeren depressiven Symptomatik zum Post-Messzeitpunkt führten. Eine weitere IPD-MA für Personen mit majorer Depression (Studie 3) identifizierte darüber hinaus ein geringes Bildungsniveau als Risikofaktor für eine Symptomverschlechterung. Die Ergebnisse des RCT (Studie 1) lassen vermuten, dass für TeilnehmerInnen mit vorangehender Psychotherapieerfahrung Online-Psychoedukation bereits hilfreich ist, während diese Maßnahme für Therapie-Neulinge keinen Nutzen zeigt, sie aber erheblich von der internetbasierten Intervention zur Behandlung ihrer Symptome profitieren. Weitere Forschung hinsichtlich einer möglichen Individualisierung internetbasierter Interventionen erscheint sinnvoll.

Angesichts der zunehmenden Nutzung internetbasierter Maßnahmen zur Behandlung von depressiven Symptomen erscheint es erforderlich, das Augenmerk neben dem Behandlungsnutzen auch auf die unerwünschten Nebenwirkungen zu lenken, für deren Berichterstattung und Handhabung es in diesem Forschungsfeld bisher kaum einen Konsens gibt. Die IPD-MA zur Behandlung von majoren Depressionen (Studie 3) konnte zeigen, dass das Risiko für eine reliable Verschlechterung von der Ausgangssituation bis zum Post-Messzeitpunkt in der Interventionsgruppe im Vergleich zur Kontrollgruppe signifikant geringer war. Eine langfristige Überlegenheit ließ sich nicht konsistent bestätigen. Der RCT (Studie 1) zeigte keinen signifikanten Unterschied in den Verschlechterungsraten zwischen den beiden Versuchsgruppen. In Studie 2 war die Interventionsgruppe der Kontrollgruppe zum Post-Messzeitpunkt und nach 12 Monaten hinsichtlich einer Symptomsteigerung um 50 % überlegen. Wie negative Effekte von internetbasierten Maßnahmen zukünftig idealerweise definiert und berichtet werden sollten, bedarf weiterer Klärung.

Es ist anzunehmen, dass internetbasierte Interventionen für die meisten Betroffenen zu einem Behandlungserfolg führen und die TeilnehmerInnen keinem höheren Risiko für eine Symptomverschlechterung ausgesetzt sind als wenn sie an keiner Maßnahme teilnehmen würden.

1.2 Abstract

Depression plays an important role in the field of mental health research due to the severe quality of life loss when suffering from depressive symptoms and the high prevalence rates. As a result of increasing digitalization, it seems obvious to treat depressive disorders also with the help of Internet-based interventions - with the aim to offer these treatments to affected individuals in addition to traditional psychotherapy and to overcome treatment barriers.

There is already a great body of evidence for the effective use of Internet-based interventions - both for patients with major depression and for people with subthreshold depression. To date, however, there is only limited evidence as to whether Internet-based interventions for the treatment of major depression are superior as well when compared to active control conditions. A randomized controlled trial (RCT) to compare an internet-based intervention with online psychoeducation only (Study 1) showed that this is indeed the case. In addition, the findings for individuals with subclinical depressive symptoms are inconsistent with regard to their long-term efficacy. An individual participant data meta-analysis (IPD-MA) to evaluate the effectiveness of Internet-based measures for the treatment of subclinical depressive symptoms (Study 2) led to a short-, medium- and long-term superiority of the treatment group compared to the control group. However, an additional analysis showed that the risk of developing major depression within 12 months in the intervention group was 28 % lower than in the control group. For the implementation of internet-based measures in routine care, it may be necessary to invest some extra effort in order to achieve comparably high effects among affected individuals.

The identification of factors influencing the success of treatment is of great interest in order to provide Internet-based measures to suitable populations in a cost-effective manner and with maximum benefit. The

IPD-MA for individuals with subthreshold depression (Study 2) showed that a high initial symptom severity and higher age led to a lower depressive symptomatology at post-measurement. Another IPD-MA for individuals with major depression (Study 3) also identified a low level of education as a risk factor for symptom deterioration. Furthermore, the results of the RCT (Study 1) suggest that while online psychoeducation is helpful for participants with previous psychotherapy experience, the superiority of the internet-based intervention over online psychoeducation seems specific for those who have no psychotherapy experience. Further research on a possible individualization of Internet-based interventions seems useful.

In view of the increasing use of Internet-based interventions for the treatment of depressive symptoms, it seems necessary to focus attention not only on the benefit of treatment but also on the undesirable side effects, for the reporting and handling of which there is so far hardly any consensus in this field of research. The IPD-MA for the treatment of major depression (Study 3) was able to show that the risk of a reliable deterioration from baseline to post-measurement time was significantly lower in the intervention group compared to the control group. The long-term superiority could not be confirmed consistently, though. The RCT (Study 1) did not show significant difference in the rates of deterioration between the two groups. In study 2, the intervention group was superior to the control group in terms of a 50 % symptom increase at posttreatment assessment and after 12 months. It needs further clarification how negative effects of internet-based measures should be defined and reported.

It can be assumed that Internet-based interventions lead to treatment success for most patients and participants are not exposed to a higher risk of symptom deterioration compared to not taking part in any intervention.

2. HINTERGRUND

Depressionen sind psychische Störungen, die mit gedrückter Stimmung, Interessenverlust, Antriebslosigkeit, Schlafstörungen und weiteren Symptomen an fast jedem Tag in einem Zeitraum von mindestens zwei Wochen einhergehen [1]. Durch eine majore Depression (MDD = major depressive disorder) können substanzielle Einschränkungen [2,3] sowie ein Verlust der Lebensqualität [4–6] entstehen. Depressive Menschen haben Schwierigkeiten, alltägliche Aufgaben zu bewältigen, leiden an Konzentrationsschwierigkeiten und starken Selbstzweifeln. Depressionen gehören zu den am weitesten verbreiteten psychischen Störungen mit Prävalenzraten von 16 % [7–11] und jährlichen Inzidenzraten von 3 % [12], die jedoch erwartungsgemäß weiterhin ansteigen werden [13]. Es wird angenommen, dass depressive Störungen bis 2030 für den höchsten Leidensdruck in Hochlohnländern verantwortlich sein werden [14]. Auch verursachen sie hohe ökonomische Kosten [15–17].

Zahlreiche Studien belegen die Wirksamkeit für verfügbare psychologische und pharmakologische Behandlungen [18,19]. Mehrere hundert Studien der vergangenen Jahre haben gezeigt, dass verschiedene Arten von Psychotherapie bei Erwachsenen bei der Behandlung von Depressionen wirksam sind. Dazu zählen beispielsweise die kognitive Verhaltenstherapie [20], Verhaltensaktivierung [21], Interpersonelle Psychotherapie [22], Problemlösen [23], nicht-direktive Beratung [24] und die psychodynamische Therapie [25]. Es konnte gezeigt werden, dass diese Therapien verglichen mit Wartelisten, Routineversorgung (TAU = treatment as usual oder CAU = care as usual) oder Medikamenten-Placebo effektiver [26] und verglichen mit medikamentösen Therapien ebenso effektiv sind [27–29].

Trotzdem bleiben viele Betroffene unbehandelt [10,30–34]. Die Gründe hierfür sind vielfältig. Beispielsweise haben viele, die von einer Behandlung profitieren würden, kein oder nur mangelhaftes Wissen über Behandlungsmöglichkeiten. Sie befürchten negative (soziale) Konsequenzen, leben in unterversorgten Regionen, fürchten mögliche Kosten oder bevorzugen Selbsthilfe [31]. Eine begrenzte Erreichbarkeit der Therapeuten und Schwierigkeiten, Termine währen der regulären Behandlungszeiten wahrzunehmen, sind weitere Barrieren [35]. Diejenigen, die sich um Hilfe bemühen, haben unter Umständen mit langen Wartezeiten zu rechnen bis Therapieplätze verfügbar sind [31,36]. Personen mit einem dringenden Bedarf an Unterstützung unversorgt zu lassen, geht mit ethischen, praktischen und therapeutischen Bedenken einher, denn dieser Umstand kann durchaus zu einer Verschlimmerung der depressiven Symptomatik und dann zu verlängerten und erschwerten Behandlungen führen [37,38].

Doch nicht nur voll ausgeprägte Depressionen beeinträchtigen die Lebensqualität, sondern auch bereits depressive Symptome, die in ihrer Gesamtheit nicht den Kriterien einer majoren Depression genügen. Auf diese Weise werden subklinische Depressionen definiert (sD = subthreshold depression) [39]. Sie sind wie MDD eine weit verbreitete Erkrankung [40], die ebenso mit einer Verschlechterung der Lebensqualität [41], einer erhöhten Mortalität [42], einer erhöhten Inanspruchnahme von Gesundheitsdienstleistungen [43] und erheblichen wirtschaftlichen Kosten [44] einhergehen. Darüber hinaus wurden subklinische Depressionen als signifikanter Prädiktor für das Auftreten einer majoren Depression identifiziert [45]. Aus diesem Grund

gilt die Aufmerksamkeit zunehmend häufiger der Prävention von Entstehungen majorer Depressionen [46,47]. Es gibt bereits meta-analytische Evidenz für die Effektivität von psychologischen Interventionen, die das (Wieder-) Auftreten von depressiven Episoden verhindern sollen [48,49]. Dabei sind insbesondere indizierte Präventionsangebote, die auf die Behandlung subklinischer Depressionen abzielen, wirksam [50]. Aufgrund begrenzter personeller und finanzieller Ressourcen können derartige Präsenzangebote jedoch nur in begrenztem Umfang angeboten werden [51,52] und zeichnen sich darüber hinaus durch niedrige Teilnehmerquoten aus [53].

3. Darstellung des Dissertationsvorhabens

3.1 Effektivität internetbasierter Maßnahmen für Personen mit depressiven Symptomen

Die Benutzung des Internets zur Behandlung von depressiven Symptomen könnte einige der zuvor genannten Barrieren aufheben, die therapeutische Maßnahmen für viele Betroffene bedeuten, denn es bietet viele Vorteile: Betroffene können ihre Behandlung in der Regel umgehend beginnen anstatt Wartezeiten zu erleben, die Programme können rund um die Uhr an allen Tagen der Woche genutzt werden – unabhängig von psychotherapeutischen Sprechzeiten, die Inhalte werden konserviert und können je nach Programm wiederholt betrachtet oder gar erneut bearbeitet werden, die TeilnehmerInnen können sie in ihrer gewohnten Umgebung durchlaufen – ohne Reisekosten oder -zeiten [54,55]. Es ist bekannt, dass derartige Maßnahmen bei Betroffenen gut akzeptiert sind [56]. Darüber hinaus stellen diese Angebote eine kosteneffektive Behandlungsalternative dar [57], mit der darüber hinaus auch Personen erreicht werden können, die bis dato unerreicht blieben [58].

Auch für den Bereich der indizierten Prävention bietet das Internet entsprechende Lösungen: Die Angebote sind weniger ressourcenintensiv und reduzieren darüber hinaus die Reisezeiten und -kosten für Teilnehmende. Sie stellen ein niedrigschwelliges Hilfsangebot dar [59] und können auch als Einstiegsintervention verstanden werden [60].

Es gibt vielfältige meta-analytische Evidenz, um die Wirksamkeit internetbasierter Maßnahmen zu belegen, sowohl für Personen mit majorer Depression [61,62] als auch für Personen mit subklinischen depressiven Beschwerden [63,64].

Im Fall von majoren Depressionen zeigen die Vorher-Nachher-Vergleiche von TeilnehmerInnen an internetbasierten Maßnahmen moderate bis hohe Effekte von Hedges‘ g = 0,64 bis g = 2,24 sowie Vorteile im Vergleich mit Kontrollgruppen (g = 0,90) [61]. Eine Kritik an aktuellen Studien kann jedoch lauten, dass internetbasierte Maßnahmen häufig mit sehr schwachen Kontrollbedingungen (meistens Wartekontrollgruppen) verglichen werden. Zu diesem Zeitpunkt der Forschung, an dem die Wirksamkeit internetbasierter Maßnahmen hinlänglich erwiesen ist, tragen derartige Studien nur noch wenig zum Wissensstand bei [65]. Somit sind aktivere Kontrollbedingungen wünschenswert. Das Internet ist für Menschen mit psychischen Beschwerden ohnehin in den meisten Fällen die erste Quelle, an der sie nach Informationen suchen, so dass eine Online-Psychoedukation eine Maßnahme darstellen kann, die einer realistischen Bedingung gleichkommt, die wir im Alltag erleben [66]. Es wurde bereits in zahlreichen Studien gezeigt, dass Online-Psychoedukation ebenfalls kleine bis mittlere Effekte von Cohen’s d = 0,29 bis d = 0,65 im Vorher-Nachher-Vergleich erzielt [67–70]. Vergleiche zwischen internetbasierter kognitiver Verhaltenstherapie (KVT / iCBT = internetbased cognitive behavioural therapy) und Online-Psychoedukation (OPE = online psychoeducation) zur Behandlung von Depressionen bei Erwachsenen sind jedoch bislang nur

wenig angestellt worden. Bisherige Ergebnisse zeigen ein gemischtes, aber tendenziell positives Bild. Beiwinkel et al. haben Effekte zugunsten der Interventionsgruppe, verglichen mit der Kontrollgruppe, von d = 0,41 bis 0,55 gefunden, als sie ein 12-Wochen-Programm, basierend auf iCBT, Achtsamkeit und systemischen Bestandteilen mit Psychoedukation verglichen [67]. In den randomisiert-kontrollierten Studien (RCTs = randomized controlled trials) von Nobis et al. (iCBT für Personen mit depressiven Symptomen und Diabetes) und Buntrock et al. (iCBT für subklinische Depressionen) waren die gefundenen Zwischen-Gruppen-Effekte sogar noch höher mit d = 0,89 [69] und d = 0,69 [71]. Christensen et al. haben in einer dreiarmigen Vergleichsstudie keinen Vorteil von iCBT gegenüber Online-Psychoedukation gefunden, während beide Interventionen jedoch einem Aufmerksamkeits-Placebo überlegen waren [72]. Letztere Ergebnisse sind allerdings mehr als 15 Jahre alt und aufgrund der technischen Weiterentwicklung inzwischen vermutlich nur noch begrenzt aussagekräftig.

Im Bereich der subklinischen depressiven Symptome gibt es deutlich weniger Forschung als für voll ausgeprägte Depressionen, dennoch wurden mehrere Studien und auch Meta-Analysen durchgeführt. Deady et al. fanden eine standardisierte Mittelwertsdifferenz (SMD = standardized mean difference) von SMD = 0,25 [73]. Der gefundene Gruppenunterschied bei Zhou et al. war in etwa gleich hoch mit SMD = 0,28 [64] und bei Sander et al. sogar etwas höher mit SMD = 0,35 [63]. Jedoch sind die Belege für die langfristige Wirksamkeit inkonsistent, da einige RCTs eine Überlegenheit für internetbasierte Programme gegenüber den Kontrollbedingungen beim Follow-Up zeigen [71,74], während andere dies nicht tun [68,75,76]. Hinsichtlich der Frage, ob die Entstehung einer MDD durch die Teilnahme an einer internetbasierten Maßnahme verhindert werden kann, gibt es bisher nur wenig Evidenz, jedoch mit vielversprechenden Ergebnissen, die Gefährdungsquoten von 0,22 [77] bis 0,59 [70] zeigen.

Hieraus ergibt sich als erstes Kernthema der vorliegenden Dissertation die Effektivität internetbasierter Maßnahmen für Personen mit depressiven Symptomen, mit den folgenden Forschungsfragen:

- Sind internetbasierte Maßnahmen für Personen mit MDD ausreichend effektiv, um einer aktiven Kontrollbedingung überlegen zu sein? (**Studie 1**)
- Gibt es kurz- und langfristige Effekte zugunsten der TeilnehmerInnen an internetbasierten Maßnahmen für subklinische Depressionen und können internetbasierte Maßnahmen das Auftreten einer MDD verhindern? (**Studie 2**)

3.2 Faktoren für den Behandlungserfolg internetbasierter Maßnahmen

Obwohl die Wirksamkeit von internetbasierten Interventionen zur Behandlung von depressiven Symptomen empirisch relativ gut belegt ist, ist nur wenig darüber bekannt, welche Personen von ihnen profitieren und welche nicht. Jedoch wäre eine Identifizierung von Faktoren, die den Behandlungserfolg beeinflussen, aus mehreren Gründen von großem Interesse: Auf diese Weise könnten geeignete Populationen für spezifische Maßnahmen ermittelt, die Inhalte der Interventionen auf die Bedürfnisse der Zielgruppen zugeschnitten und monetäre Mittel evidenzbasiert und kosteneffektiv eingesetzt werden [78]. Inzwischen wird diesem

Thema in der Forschung zunehmend mehr Beachtung geschenkt. Jedoch lassen sich bisher nur begrenzt gesicherte Aussagen treffen, denn häufig können die gewünschten Eigenschaften im Rahmen von Moderatoranalysen in Einzelstudien nicht angemessen untersucht werden, weil der Stichprobenumfang in der Regel so bemessen ist, dass sich der Gesamtbehandlungseffekt bestimmen lässt, spezifische Subgruppen jedoch nicht analysiert werden können. Es ist dennoch anzunehmen, dass nicht alle Untergruppen von Betroffenen im gleichen Maße von dieser spezifischen Behandlungsform profitieren. Bisher liefern, wie im Folgenden dargestellt, zahlreiche Einzelstudien Hinweise auf mögliche Risikofaktoren, die mit der Entstehung einer Depression in Verbindung gebracht werden können. Allerdings wurden bislang wenige Untersuchungen darüber angestellt, welche Faktoren den Behandlungserfolg moderieren. Häufig werden nur Prädiktoren / Risikofaktoren identifiziert und berichtet. Es kann unterschieden werden zwischen demografischen und klinischen Faktoren sowie Faktoren auf Studienebene, die im Folgenden beispielhaft und ohne Anspruch auf Vollständigkeit dargestellt werden sollen:

Demografische Faktoren

Das weibliche Geschlecht hat sich im Rahmen epidemiologischer Forschung unabhängig von kulturellen Hintergründen als Risikofaktor für die Entstehung einer Depression erwiesen. Zur Erklärung des höheren Depressionsrisikos werden genetische, hormonelle, psychologische sowie psychosoziale Ursachen angeführt [79]. Auch für sehr spezifische Zielgruppen ließ sich das weibliche Geschlecht als Risikofaktor identifizieren: So zeigte es sich als relevant für die Entstehung einer Depression bei argentinischen Krankenhauspatienten [80] und auch im Allgemeinen während der Adoleszenz [81], während in einer Stichprobe von serbischen Medizinstudenten kein Zusammenhang zwischen Geschlecht und Symptomschwere gefunden werden konnte [82].

Jüngeres Alter zeigte sich in einem Review als Risikofaktor für die Entwicklung einer chronischen Depression [83] sowie für eine majore Depression bei serbischen Medizinstudenten [82]. In einer jüngst veröffentlichten Meta-Analyse auf Basis von individuellen Teilnehmerdaten (IPD-MA) zur internetbasierten Behandlung von MDD erzielten ältere TeilnehmerInnen bessere Behandlungserfolge als jüngere [84]. Im Bereich von sD zeigen verschiedene Einzelstudien unterschiedliche Resultate: Brière et al. und Müller et al. konnte keinen moderierenden Effekt für Alter bei Jugendlichen finden [85,86], während Vázquez et al. zeigen konnte, dass jüngere Pflegekräfte stärker von dem untersuchten iCBT-Programm profitierten als ältere [87]. In einer randomisiert-kontrollierten Studie von Button et al. zeigte sich Alter nicht als signifikanter Moderator für den Behandlungserfolg beim Vergleich von iCBT versus Routineversorgung.

Keiner beruflichen Tätigkeit nachzugehen erwies sich als Risikofaktor für eine psychotische MDD [88]. Gleichzeitig führte das Vorhandensein einer Beschäftigung zu niedrigeren depressiven Symptomen – unabhängig davon, welche Behandlung StudienteilnehmerInnen erfahren haben [89].

Auch könnte argumentiert werden, dass es ein gewisses Bildungsniveau erfordert, internetbasierte therapeutische Selbsthilfemaßnahmen anzuwenden und dass Personen mit geringer Bildung sich davon

leicht überfordert fühlen könnten [90]. Ein niedriger Bildungsstand wurde beispielsweise als Risikofaktor für postpartale Depressionen unter Frauen in Kanada identifiziert [91].

Klinische Faktoren

Es ist denkbar, dass internetbasierte Maßnahmen in erster Linie für leichte bis moderate Depressionen erfolgversprechend sind, weil schwer depressive Teilnehmende gegebenenfalls durch ihre Symptome zu stark beeinträchtigt sind, um einen großen Behandlungseffekt zu erzielen [65]. Andererseits haben Betroffene mit stärkeren depressiven Symptomen auch ein größeres Verbesserungspotenzial. Die initiale Symptomschwere könnte wesentlich dafür verantwortlich sein, in welchem Maße TeilnehmerInnen von den Maßnahmen profitieren. In einigen Studien im Bereich MDD ließ sich zeigen, dass höhere depressive Symptome zu Beginn einer Maßnahme zu besseren Behandlungserfolgen führten [84,92,93], während eine andere Studie keinen moderierenden Effekt in Bezug auf die Symptomschwere fand [89].

Das Vorhandensein chronischer Erkrankungen zeigte sich in verschiedenen Studien als weiterer Risikofaktor für die Entwicklung einer majoren Depression [80,94,95] und Komorbiditäten für die Entwicklung einer chronischen Depression [83].

Faktoren auf Studienebene

Meta-Analysen über Studien zur internetbasierten Behandlung von MDD zeigten eine Überlegenheit der Interventionen mit einem hohen Maß an Begleitung durch einen Psychotherapeuten oder eine geschulte Person im Vergleich zu keiner oder niedriger Begleitung [62,96,97].

Richards und Richardson fanden darüber hinaus deutlich höhere Effekte für Programme mit weniger als acht Lektionen verglichen mit acht oder mehr Lektionen bei TeilnehmerInnen mit MDD [62], während Cuijpers et al. im Forschungsfeld der subklinischen Depressionen keinen signifikanten Zusammenhang zwischen der Anzahl der Lektionen und der Inzidenzrate für die Entstehung einer majoren Depression fanden [98].

Darüber hinaus könnte es auch einen Unterschied machen, ob Teilnehmende an internetbasierten Maßnahmen zuvor bereits Erfahrung mit psychotherapeutischen Maßnahmen gemacht haben. Dieser Fall wäre in diesem Zusammenhang nicht ungewöhnlich, denn aufgrund der hohen Prävalenz [7,10] und der Chronizität depressiver Erkrankungen [99] ist MDD generell für eine hohe Inanspruchnahme von Gesundheitsdienstleistungen verantwortlich [100–102]. Die Forschung über die Auswirkungen einer vorangegangenen Psychotherapie auf den Erfolg einer weiteren Maßnahme ist bisher nicht sehr fortgeschritten und zeigt unterschiedliche Resultate: Eine Studie zeigte eine höhere Wahrscheinlichkeit für eine signifikante Veränderung depressiver Symptome, wenn Menschen keine Vorgeschichte der Inanspruchnahme von psychologischen Diensten hatten [103], während andere Studien keine signifikanten Zusammenhänge zwischen früherer Psychotherapie und Behandlungseffektivität fanden [93,104,105].

Moderatoren für den Behandlungserfolg im Sinne einer Symptomreduzierung oder der Verhinderung der Entstehung einer voll ausgeprägten Depression beim Vorliegen von subklinischen Symptomen sind bisher nur wenig erforscht. Noch weniger erforscht ist die Frage, für welche der TeilnehmerInnen ein höheres Risiko besteht, gar eine Symptomverschlechterung zu erfahren. Dies liegt unter anderem daran, dass die Zahlen der Personen, deren Symptome sich verschlechtern, im Allgemeinen sehr gering sind und darüber hinaus die meisten randomisiert-kontrollierten Studien hinsichtlich ihrer Teilnehmerzahlen nicht auf die Analyse von Moderatoreffekten ausgelegt sind [106]. Jedoch erscheint es dringend erforderlich zu untersuchen, für welche TeilnehmerInnen diese spezifische Behandlungsform schädlich sein könnte und Risikogruppen zu identifizieren, für die eine Symptomverschlechterung wahrscheinlich ist, mit dem Ziel, ihnen angemessenere Behandlungsmethoden zukommen zu lassen.

Hieraus ergeben sich die Faktoren für den Behandlungserfolg internetbasierter Maßnahmen als zweites Kernthema dieser Dissertation, mit folgenden Forschungsfragen:

- Welche Faktoren beeinflussen den Behandlungserfolg für Personen mit subklinischen Depressionen? (**Studie 2**)
- Für welche TeilnehmerInnen mit MDD besteht das Risiko einer Symptomverschlechterung? (Studie 3)
- Hat vorangehende Psychotherapieerfahrung einen Einfluss auf den Behandlungserfolg für Personen mit MDD? (Studie 1)

3.3 Nebenwirkungen von internetbasierten Maßnahmen

Die Psychotherapie-Ergebnisforschung konzentriert sich natürlicherweise in erster Linie auf den Behandlungsnutzen [107], dabei kann iCBT wie jede andere potenziell wirksame Behandlung auch zu unerwünschten Ergebnissen oder Nebenwirkungen führen. Es ist nicht ausgeschlossen, dass Betroffene auch Schaden durch ihre Behandlung erfahren [108]. In der pharmakologischen Forschung ist es Standard, stets sowohl Risiken als auch Nutzen einer Intervention zu bewerten [109,110]. Für die Psychotherapieforschung, insbesondere für internetbasierte Behandlungen gibt es bisher jedoch nur wenig Einigkeit darüber, wie Schaden gemessen werden kann und wie zu handeln ist, wenn er entsteht [107,108]. Insgesamt berichten nur etwa die Hälfte der psychotherapeutischen Studien auch die unerwünschten Ergebnisse [111,112]. Dabei ist die Frage nach den negativen Auswirkungen relevant für die Behandlungsentscheidung. Es könnte argumentiert werden, dass Selbsthilfemaßnahmen für Individuen mit sehr schweren Symptomen möglicherweise nicht intensiv genug sind [65,113], die meisten Selbsthilfemaßnahmen nicht auf den aktuellen Zustand des einzelnen zugeschnitten sind, nicht überwacht werden und daher auch nicht auf eine Symptomverschlechterung reagieren können [114,115].

Unter den verschiedenen möglichen negativen Auswirkungen der Psychotherapie ist ein besonders ungünstiges Ergebnis die Verschlechterung der Symptome als Folge der Behandlung. Evidenz aus unkontrollierten Psychotherapie-Ergebnisstudien zeigt, dass eine beträchtliche Anzahl von Patienten

während ihrer Psychotherapie eine Verschlechterung der Symptome erlebt. Der Anteil der Patienten mit Symptomverschlechterung in diesen unkontrollierten Studien liegt zwischen 3 und 14 % [116–119]. Dieses Phänomen des "Verschlechterungseffekts" wurde bereits in den ersten Jahren der Psychotherapieforschung beobachtet [120,121]. In Hinblick auf internetbasierte Selbsthilfebehandlungen könnte man argumentieren, dass solche Interventionen mit einem noch größeren Risiko für eine Verschlechterung der Symptome verbunden sein können als klassische Face-to-Face Ansätze. Darüber hinaus können Einzelpersonen überfordert sein, wenn sie versuchen, psychotherapeutische Selbsthilfe-Strategien anzuwenden. Einige therapeutische Techniken könnten von den TeilnehmerInnen ohne direkte Anleitung durch den Therapeuten unsachgemäß eingesetzt werden, was zu einer weiteren Verschärfung der Hoffnungslosigkeit bei schwer betroffenen Personen führen könnte. Es könnte auch argumentiert werden, dass es bei Face-to-Face-Behandlungen deutlich einfacher ist, erste Anzeichen einer Verschlechterung zu beobachten und darauf zu reagieren als über das Internet. Obwohl die Themen der möglichen negativen Auswirkungen sowohl der internetbasierten Behandlungen [11,65,122,123] als auch der individuellen Psychotherapie [107,108,124–126] in jüngster Zeit in der Literatur an Aufmerksamkeit gewonnen haben, fehlen empirische Belege für mögliche negative Effekte aus randomisiert-kontrollierten Studien noch fast vollständig [107]. Dies ist sowohl für MDD als auch für sD zutreffend.

Neben den Fällen von Symptomverschlechterung gibt es nur sehr wenige Studien, die darüber hinaus negative Auswirkungen auf die Einstellung zur zukünftigen Inanspruchnahme von psychotherapeutischen Angeboten und andere unerwünschte Nebeneffekte wie beispielsweise die Steigerung von Suizidabsichten berichten [122,127], so dass eine weitere Analyse verschiedener negativer Effekte angesichts der zunehmenden Nutzung internetbasierter Interventionen unumgänglich scheint [11,122,128].

Letztlich stellen die Nebenwirkungen von internetbasierten Maßnahmen das dritte Kernthema dieser Dissertation dar, mit folgenden Forschungsfragen:

- Kann die Teilnahme an internetbasierten Interventionen zur Behandlung von MDD zu einer signifikanten Symptomverschlechterung führen? (**Studie 3** und Studie 1)
- Kann die Teilnahme an einer internetbasierten Intervention zur Behandlung von MDD darüber hinaus zu weiteren unerwünschten Nebenwirkungen führen? (Studie 1)
- Kann die Teilnahme an internetbasierten Interventionen zur Behandlung von sD zu einer signifikanten Symptomverschlechterung führen? (Studie 2)

4. ZUSAMMENFASSUNG DER STUDIEN

Im Rahmen dieser Dissertation wurden drei Studien durchgeführt, die dazu herangezogen werden können, die drei zuvor benannten Kernthemen differenziert zu beantworten. Zu den drei durchgeführten Studien zählen: 1) eine randomisiert-kontrollierte Studie zur Analyse einer spezifischen internetbasierten Maßnahme zur Behandlung von MDD im Vergleich zu Online-Psychoedukation; 2) eine IPD-Meta-Analyse zur Wirksamkeit internetbasierter Maßnahmen zur Behandlung von subklinischen Depressionen mit dazugehörigem Studienprotokoll sowie 3) eine IPD-Meta-Analyse zur Untersuchung von Verschlechterungsraten bei internetbasierten Maßnahmen zur Behandlung von MDD. Die Studien mit den dazugehörigen Forschungsfragen sollen im folgenden Abschnitt zunächst tabellarisch und dann in Form einer kurzen Zusammenfassung dargestellt werden.

Studie	**Studie 1: The more I got, the less I need? Efficacy of Internet-based guided self-help compared to online psychoeducation for major depressive disorder**	**Studie 2: Efficacy and moderators of internet-based interventions in adults with subthreshold depression – an individual participant data meta-analysis of randomized controlled trials**	**Studie 3: Does Internet-based guided-self-help for depression cause harm? An individual participant data meta-analysis on deterioration rates and its moderators in randomized controlled trials**
Art der Studie	RCT	IPD-MA	IPD-MA
Zielgruppe	Personen mit MDD	Personen mit sD	Personen mit MDD
Stichprobengröße	131	2186	2079
Kernthema 1) Effektivität internetbasierter Maßnahmen für Personen mit depressiven Symptomen	Sind internetbasierte Maßnahmen für Personen mit MDD ausreichend effektiv, um einer aktiven Kontrollbedingung überlegen zu sein?	Gibt es kurz- und langfristige Effekte zugunsten der TeilnehmerInnen an internetbasierten Maßnahmen für subklinische Depressionen und können internetbasierte Maßnahmen das Auftreten einer MDD verhindern?	
Kernthema 2) Faktoren für den Behandlungserfolg	Hat vorangehende Psychotherapieerfahrung einen Einfluss auf den Behandlungserfolg für Personen mit MDD?	Welche Faktoren beeinflussen den Behandlungserfolg für Personen mit subklinischen Depressionen?	Für welche TeilnehmerInnen mit MDD besteht das Risiko einer Symptomverschlechterung?
Kernthema 3) Nebenwirkungen von internetbasierten Maßnahmen	Kann die Teilnahme an internetbasierten Interventionen zur Behandlung von MDD zu einer signifikanten Symptomverschlechterung führen? Kann die Teilnahme an einer internetbasierten Intervention zur Behandlung von MDD darüber hinaus zu weiteren unerwünschten Nebenwirkungen führen?	Kann die Teilnahme an internetbasierten Interventionen zur Behandlung von sD zu einer signifikanten Symptomverschlechterung führen?	Kann die Teilnahme an internetbasierten Interventionen zur Behandlung von MDD zu einer signifikanten Symptomverschlechterung führen?

4.1 Studie 1: The more I got, the less I need? Efficacy of Internet-based guided self-help compared to online psychoeducation for Major Depressive Disorder

Hintergrund: Viele randomisiert-kontrollierte Studien vergleichen internetbasierte Maßnahmen mit passiven Kontrollbedingungen (z.B. Wartelisten). Diese Vergleiche tragen zum aktuellen Wissensstand nur wenig bei, da die Wirksamkeit bereits hinlänglich bewiesen ist. Da viele Betroffene heutzutage zunächst Hilfe im Internet suchen, z.B. indem sie sich über Symptome informieren, stellt eine Online-Psychoedukation eine realistische aktive Vergleichsbedingung dar. Ziel dieser Studie war es, die Wirksamkeit und die negativen Auswirkungen einer begleiteten internetbasierten Selbsthilfemaßnahme auf Basis der kognitiven Verhaltenstherapie (iCBT) und einer Online-Psychoedukation (OPE) bei Menschen mit Depressionen zu vergleichen.

Methoden: Insgesamt wurden 131 Personen mit MDD entweder in die iCBT-Gruppe (n = 65) oder in die OPE-Gruppe (n = 66) randomisiert. Die Erhebungen erfolgten zu Studienbeginn (T1), nach sechs Wochen (T2) und nach drei Monaten (T3). Das primäre Ergebnis war eine Veränderung der Depressionsschwere von T1 bis T2 per Fremdeinschätzung mit der Hamilton Rating Scale for Depression (HRSD-24). Darüber hinaus wurden weitere Daten zur mentalen und physischen Gesundheit (selbst eingeschätzte Depression, Angst, Lebensqualität, Problemlösekompetenz, Verhaltensaktivierung, psychologisches Wohlbefinden) erhoben. Mögliche negative Auswirkungen wurden in Form von Selbstmordgedanken, Symptomverschlechterung, Einstellung zur Inanspruchnahme von Psychotherapie und anderen unerwünschten Ereignissen analysiert.

Ergebnisse: Sowohl die iCBT-TeilnehmerInnen als auch die OPE-TeilnehmerInnen reduzierten ihre depressiven Symptome von T1 bis T2 mit großen Effekten für iCBT (Cohen's d = 1,09) und mittleren Effekten für OPE (d = 0,60). Die Gruppen unterschieden sich zu T2 signifikant voneinander (d = 0,36, p = 0,028). OPE entwickelte sich bis T3 weiterhin positiv, während der Effekt für iCBT stabil blieb. Die Unterschiede zwischen den Gruppen waren zu T3 nicht mehr signifikant. Teilnehmende, die sich vorher einer Psychotherapie unterzogen hatten, profitierten von beiden Behandlungen; für diejenigen ohne vorherige Psychotherapie war iCBT jedoch überlegen. ICBT war gegenüber OPE hinsichtlich der selbst eingeschätzten Depression, Verhaltensaktivierung und Angst für die Veränderung von T1 zu T2 im Vorteil. Für die Veränderung von T1 bis T3 war iCBT der OPE-Bedingung hinsichtlich Verhaltensaktivierung und psychisches Wohlbefinden überlegen. Die Suizidalitäts-Prävalenz blieb in beiden Gruppen zwischen den Messzeitpunkten stabil. Es gab keine Gruppenunterschiede hinsichtlich der Verschlechterungsraten sowie der Einstellung gegenüber einer möglichen zukünftigen Inanspruchnahme von psychotherapeutischen Angeboten. 26,2 % der TeilnehmerInnen in der iCBT-Gruppe berichteten mindestens einen weiteren Nebeneffekt.

Schlussfolgerungen: iCBT ist effektiver bei der Reduzierung depressiver Symptome als Online-Psychoedukation, insbesondere bei Betroffenen ohne Psychotherapieerfahrung. Negative Effekte treten bei einem erheblichen Teil der Menschen auf und sollten sowohl in zukünftigen Studien als auch bei der Implementierung von iCBT berücksichtigt werden.

4.2 Studie 2 – Protokoll: Efficacy and moderators of psychological interventions in treating subclinical symptoms of depression and preventing major depressive disorder onsets: protocol for an individual patient data meta-analysis of randomised controlled trials

Hintergrund: Die langfristige Wirksamkeit von psychologischen Interventionen zur Behandlung von subklinischen Depressionen und zur Verhinderung der Entstehung einer majoren Depression ist unklar und die Effekte variieren für verschiedene Subgruppen von Patienten, was darauf hindeutet, dass nicht alle Patienten von solchen Interventionen profitieren. Randomisiert-kontrollierte klinische Studien sind hinsichtlich ihrer Power-Planung meist nicht darauf ausgelegt, Subgruppen und Moderatoreffekte adäquat zu untersuchen. Ziel der vorliegenden Studie ist daher die Untersuchung der kurz- und langfristigen Wirksamkeit sowie der Moderatoreffekte psychologischer Interventionen im Vergleich zu Kontrollgruppen bei Erwachsenen mit depressiven Symptomen in Bezug auf depressive Symptomschwere, positive Behandlungsreaktionen, Beschwerdefreiheit, Symptomverschlechterung, Lebensqualität, Angst und die Prävention schwerer depressiver Störungen auf individueller Patienten- und Studienebene mit einer Meta-Analyse auf Basis der individuellen Patientendaten.

Methoden und Analysen: Es werden systematische Suchen in PubMed, PsycINFO, Embase und im Cochrane Zentralregister für kontrollierte Studien durchgeführt. Folgende Ergebniskriterien sollen verwendet werden: (A) Entstehung einer majoren Depression; (B) Zeit bis zum Beginn dieser majoren Depression; (C) fremd- und selbstbewertete Schwere der depressiven Symptome; (D) positive Behandlungsreaktion; (E) Beschwerdefreiheit; (F) Symptomverschlechterung; (G) Lebensqualität, (H) Angst und (I) Selbstmordgedanken und -handlungen. Es wird ein Multilevel-Ansatz verfolgt. Fehlende Daten werden mithilfe multipler Imputationsverfahren ersetzt. Mehrere Sensitivitätsanalysen werden durchgeführt, um die Robustheit der gefundenen Ergebnisse zu testen.

Ethik und Verbreitung: Diese Studie wird die verfügbare Evidenz für die kurz- und langfristigen Effekte von präventiven psychologischen Interventionen zur Behandlung von depressiven Beschwerden und zur Verhinderung der Entstehung einer Depression zusammenfassen. Die Identifikation von Subgruppen, für die derartige Interventionen am effektivsten sind, wird die Entwicklung von evidenzbasierten personalisierten Interventionen für Patienten mit subklinischen Depressionen vorantreiben.

4.3 Studie 2: Efficacy and moderators of internet-based psychological treatments in adults with subthreshold depression – an individual patient data meta-analysis of randomized controlled trials

Hintergrund: Subklinische Depressionen (sD) gehen mit einer hohen Prävalenz, einer niedrigeren Lebensqualität, einem erhöhten Risiko, eine majore Depression (MDD) zu entwickeln sowie einer erhöhten

Inanspruchnahme von Gesundheitsdienstleistungen einher. Die Evidenz über die Auswirkungen internetbasierter Interventionen zur Behandlung von subklinischen Depressionen und zur Verhinderung des Auftretens von majoren Depressionen ist inkonsistent. Im Rahmen einer individuellen Teilnehmerdaten-Meta-Analyse (IDP-MA) wurden Unterschiede zwischen Interventions- und Kontrollgruppen hinsichtlich depressiver Symptomschwere, positiver Behandlungsreaktion, Beschwerdefreiheit, Symptomverschlechterung und Entstehung einer MDD ermittelt. Darüber hinaus wurden Moderatoren von Interventionsergebnissen untersucht.

Methoden: Randomisierte kontrollierte Studien zur Evaluation von internetbasierten Interventionen zur Behandlung von Erwachsenen mit subklinischen depressiven Symptomen wurden durch systematische Recherchen über PubMed, PsycINFO, Embase und Cochrane Library identifiziert. Mehrebenen-Regressionsanalysen wurden zur Überprüfung der Effektivität und der Moderatoren eingesetzt. Fehlende Daten wurden mehrfach imputiert.

Ergebnisse: Sieben Studien (n = 2186 TeilnehmerInnen) wurden für die Analysen berücksichtigt. Die Ergebnisse zeigten Gruppeneffekte zugunsten der Interventionsgruppe zum Post-Messzeitpunkt (6 - 12 Wochen; Hedges' g = 0,39 [95 % KI: 0,25 - 0,53]), zum Follow-Up 1 (3 - 6 Monate; g = 0,30 [95 % KI: 0,15 - 0,45]) und zum Follow-Up 2 (12 Monate; g = 0,27 [95 % KI: 0,07 – 0,47]). Deutlich mehr Teilnehmende der Interventionsgruppe zeigten eine positive Behandlungsreaktion oder Beschwerdefreiheit zu allen Messzeitpunkten. Das Risiko für eine Symptomverschlechterung war zum Post-Messzeitpunkt und zum Follow-Up 2 in der Interventionsgruppe signifikant geringer als in der Kontrollgruppe. Die Inzidenzraten für die Entwicklung einer MDD innerhalb von 12 Monaten waren in der Interventionsgruppe (19 %) niedriger als in der Kontrollgruppe (26 %). Das Risiko für die Entwicklung einer MDD war in der Interventionsgruppe im Vergleich zur Kontrollgruppe um 28 % geringer. Die initiale Symptomschwere und Alter wurden als Moderatoren für das Interventionsergebnis zum Post-Messzeitpunkt identifiziert, mit der Tendenz, dass höhere initiale Symptomschwere und höheres Alter zu besseren Behandlungserfolgen führten.

Schlussfolgerungen: Diese Ergebnisse belegen, dass internetbasierte Interventionen eine geeignete niedrigschwellige Intervention darstellen, um Menschen mit subklinischen Depressionen zu behandeln und das Risiko für die Entstehung einer MDD zu reduzieren. Dies gilt insbesondere für ältere Teilnehmer und für Personen, die bereits eine gewisse Symptombelastung mitbringen.

4.4 Studie 3: Does Internet-based guided-self-help for depression cause harm? An individual participant data meta-analysis on deterioration rates and its moderators in randomized controlled trials

Hintergrund: Depressionen sind nicht nur hoch prävalent, sondern auch mit erheblichen Beeinträchtigungen und hohen ökonomischen Kosten verbunden. Ihre Behandlung im Rahmen von internetbasierten Interventionen zeigte sich als effektiv, ökonomisch und von den TeilnehmerInnen gut akzeptiert. Über die

möglichen negativen Auswirkungen von internetbasierten psychologischen Behandlungen von Depressionen ist fast nichts bekannt. Diese Studie zielt darauf ab, eine mögliche Verschlechterung sowie relevante Moderatoren in randomisiert-kontrollierten Studien zu internetbasierter, begleiteter Selbsthilfe bei Depressionen bei Erwachsenen im Vergleich zu einer Kontrollgruppe mit Hilfe einer Meta-Analyse auf Basis individueller Teilnehmerdaten zu untersuchen.

Methoden: Randomisiert kontrollierte Studien zur Evaluation begleiteter internetbasierter Interventionen zur Behandlungen von Depressionen bei Erwachsenen wurden durch systematische Literaturrecherchen (PubMed, PsycINFO, EMBASE, Cochrane Library) identifiziert. Die Symptomverschlechterung bei den TeilnehmerInnen wurde als signifikanter Symptomanstieg gemäß dem Reliable Change Index definiert (entspricht 7,68 Punkten im CES-D und 7,63 Punkten im BDI). Zweistufige IPD-MA-Verfahren mit einem Random-Effects-Model wurden verwendet, um die Daten zusammenzuführen.

Ergebnisse: Insgesamt 18 Studien (21 Vergleiche, 2079 TeilnehmerInnen) trugen Daten zur Analyse bei. Das Risiko für eine reliable Symptomverschlechterung von den Ausgangswerten bis zum Post-Messzeitpunkt war in der Interventionsbedingung signifikant geringer als in der Kontrollbedingung (3,36 vs. 7,60; relatives Risiko 0,47, 95 % KI 0,29 - 0,75). Der Bildungsstand hat die Stärke der Symptomverschlechterung beeinflusst, indem Patienten mit geringer Bildung ein höheres Risiko für eine Verschlechterung aufwiesen als Patienten mit höherer Bildung. Die Verschlechterungsraten für Patienten mit geringer Bildung haben sich nicht signifikant zwischen Interventions- und Kontrollgruppen unterschieden. Die Nutzen-Risiko-Relation für Patienten mit geringer Bildung zeigte, dass pro Patient mit einer reliablen Symptomverschlechterung 9,38 Patienten eine positive Behandlungsreaktion erzielen. Es ließen sich keine weiteren Unterschiede zwischen den Subgruppen identifizieren.

Schlussfolgerungen: Verglichen mit der Kontrollbedingung sind begleitete internetbasierten Maßnahmen mit einem mittleren reduzierten Risiko für eine Symptomverschlechterung verbunden. Der Therapie- und Symptomverlauf von Patienten mit geringer Bildung sollte genau überwacht werden, da einige Patienten ein erhöhtes Risiko für eine Verschlechterung der Symptome haben könnten. Zukünftige Studien sollten die Prädiktoren der Symptomverschlechterung bei Patienten mit geringer Bildung untersuchen.

5. Ergebnisse

5.1 Effektivität Internetbasierter Maßnahmen für Personen mit depressiven Symptomen

Sind internetbasierte Maßnahmen für Personen mit MDD ausreichend effektiv, um einer aktiven Kontrollbedingung überlegen zu sein? (Studie 1)

Um die Wirksamkeit des Trainings GET.ON Mood Enhancer (iCBT) zu untersuchen, wurden 131 Personen mit vorliegender Depression (diagnostiziert nach DSM-IV) in die Studie aufgenommen. Das begleitete Selbsthilfeprogramm GET.ON Mood Enhancer wurde mit einer Online-Psychoedukationsgruppe (OPE) verglichen. Die Messungen fanden zur Baseline (T1), unmittelbar nach dem Training (nach 6 Wochen, T2) und nach 12 Wochen (T3) statt.

Im Rahmen der Primäranalyse wurden Gruppenunterschiede in der depressiven Symptomatik mithilfe eines gemischten Modells mit festen Effekten für Symptomschwere, Gruppe und Messzeitpunkt analysiert. Zusätzlich enthielt das Modell den Zweifach-Interaktionsterm Gruppe x Messzeitpunkt, um den Interventionseffekt zwischen Baseline und den beiden späteren Messzeitpunkten zu analysieren.

Beide Studiengruppen zeigten statistisch signifikante Verringerungen der beobachteten Depressionsschwere von der Baseline (T1) bis zu den Post-Messungen (T2) auf der Hamilton Rating Scale for Depression (HRSD-24 [129,130]). Die Analyse des Basismodells im Rahmen des Mixed-Effects-Modells (MEM), unbereinigt um etwaige Baseline-Ungleichgewichte, zeigte, dass bei denjenigen, die iCBT erhielten, eine mittlere Reduktion der HRSD um 8,31 Punkte zu verzeichnen war ($p < 0,001$; $d = 1,09$, 95 % KI: 0,72 - 1,46). In der OPE-Gruppe betrug die mittlere Reduktion auf der HRSD 5,42 Punkte ($p < 0,001$; $d = 0,59$, 95 % KI: 0,24 - 0,94). Beide Gruppen zeigten auch signifikante Rückgänge von T1 bis zum 3-Monats-Follow-Up (T3), von 8,62 Punkten in der iCBT-Gruppe ($p < 0,001$; $d = 1,02$, 95 % KI: 0,65 - 1,38) und 7,70 Punkten in der Psychoedukationsgruppe ($p < 0,001$; $d = 0,87$, 95 % KI: 0,51 - 1,23). Die Analyse der Gruppenunterschiede ergab eine signifikant stärkere Reduktion der Depressionsschwere von T1 bis T2 zum Vorteil von iCBT, verglichen mit OPE (T1-T2 x Gruppe: $p = 0,028$; $d = 0,36$, 95 % KI: 0,01 - 0,70). Die Veränderungsmessung von T1 zu T3 ergab keinen signifikanten Gruppenunterschied (T1-T3 x Gruppe: $p = 0,197$), das heißt die Überlegenheit nach 12 Wochen konnte nicht belegt werden.

Es gab keine signifikanten Unterschiede zwischen den beiden Behandlungsgruppen in Bezug auf den Prozentsatz der TeilnehmerInnen, die eine positive Behandlungsreaktion von T1 bis T2 ($\chi^2 = 0,420$, $p = 0,279$) oder von T1 bis T3 ($\chi^2 = 0,062$, $p = 0,402$) zeigten. Es gab auch keine signifikanten Unterschiede in den Remissionsraten zwischen den Gruppen, weder bei T2 ($\chi^2 = 0,654$, $p = 0,210$) noch bei T3 ($\chi^2 = 0,374$, $p = 0,271$). In der iCBT-Gruppe, verglichen mit der OPE-Gruppe, zeigten deutlich mehr Teilnehmende eine reliable Verbesserung der Depressionsschwere von T1 bis T2 ($\chi^2 = 5,152$, $p = 0,012$), angegeben durch eine NNT

(number needed to treat) von 5,12 (95 % KI: 2,77 - 33,11), die zur Behandlung benötigt wird, um eine zuverlässige Verbesserung von T1 bis T2 zu erreichen. Es gab keinen signifikanten Gruppenunterschied für die Veränderungsmessung von T1 bis T3 (χ^2 = 0,719, p = 0,198).

Gibt es kurz- und langfristige Effekte zugunsten der TeilnehmerInnen von internetbasierten Maßnahmen für subklinische Depressionen und können internetbasierte Maßnahmen das Auftreten einer MDD verhindern? (Studie 2)

Für die IPD-MA wurden 7 randomisiert-kontrollierte Studien mit n = 2186 TeilnehmerInnen zur Evaluation von internetbasierten Selbsthilfemaßnahmen zur Behandlung von subklinischen Depressionen gemeinsam innerhalb einer Mehrebenen-Regressionsanalyse evaluiert. Es liegen Daten zum Post-Messzeitpunkt (6 - 12 Wochen), zum Follow-Up 1 (3 - 6 Monate) und zum Follow-Up 2 (12 Monate) vor.

Die Interventionsgruppen waren den Kontrollgruppen beim Post-Messzeitpunkt (b = -3,874, 95 % KI: -5,26 - -2,49; t(17229) = -5,49, p < 0,001; Hedges' g = 0,39 [95 % KI: 0,25 - 0,53]), beim Follow-Up 1 (b = -3,028, 95 % KI: -4,53 - -1,52; t(4467) = -3,95, p < 0,001; g = 0,30 [95 % KI: 0,15 - 0,45]) und beim Follow-Up 2 (b = -2,688, 95 % KI: -4,72 - -0,66; t(549) = -2,59, p = 0,010; g = 0,27 [95 % KI: 0,07 – 0,47]) überlegen. Dieselben Ergebnismuster zeigten sich auch für eine positive Behandlungsreaktion und Beschwerdefreiheit.

Drei der sieben Studien mit n = 1583 TeilnehmerInnen (72,4 % der Gesamtstichprobe) lieferten Daten über die Entstehung einer MDD. 18,7 % der TeilnehmerInnen der Interventionsgruppe und 25,8 % der Kontrollgruppe entwickelten eine majore Depression während des Untersuchungszeitraums. Die Kaplan-Meier-Schätzungen der kumulativen Inzidenz von MDD lagen bei 26 % (95 % KI: 22 % - 30 %) für die Interventionsgruppe und 34 % (95 % KI: 30 % - 37 %) für die Kontrollgruppe. Der Log-Rank-Test ergab einen statistisch signifikanten Unterschied zwischen den Inzidenzraten im Zeitverlauf (p = 0,004). Die durchschnittliche Zeit bis zum Beginn der MDD innerhalb der 12-monatigen Studienzeit betrug 33 Wochen in der Interventionsgruppe und 32 Wochen in der Kontrollgruppe. Die Cox-Regression, die für die initiale Symptomschwere kontrolliert wurde, ergab ein Hazard Ratio von 0,72 (95 % KI: 0,58 – 0,89), was bedeutet, dass das Risiko für den Beginn einer Depression innerhalb von 12 Monaten in der Interventionsgruppe im Vergleich zur Kontrollgruppe 28 % geringer war. Die geschätzte Hazard Ratio für die Schwere der depressiven Symptome betrug 1,09 (95 % KI: 1,06 - 1,11).

5.2 Faktoren für den Behandlungserfolg internetbasierter Maßnahmen

Welche Faktoren beeinflussen den Behandlungserfolg für Personen mit subklinischen Symptomen? (Studie 2)

Prädiktoren für die Schwere der Depression und Moderatoren des Interventionseffekts wurden untersucht, indem ausgewählte Variablen auf Teilnehmer- und Studienebene sowie deren Interaktion mit der Gruppenvariablen als zusätzliche Prädiktoren in einstufigen logistischen Regressionsanalysen eingeschlossen wurden. Dafür wurden Geschlecht, Alter, Beziehungsstatus sowie Beschäftigungsstatus als soziodemografische

Merkmale analysiert. Die initiale Symptomschwere, Angstsymptome, Komorbiditäten, frühere Psychotherapien, die Einnahme von Antidepressiva sowie chronische Erkrankungen wurden als klinische Eigenschaften in die Untersuchungen einbezogen. Das Format der internetbasierten Interventionen (begleitet / unbegleitet) sowie die Programmlänge in Wochen wurden als Interventionsmerkmale auf Studienebene betrachtet. Für den Post-Messzeitpunkt haben sich unter den klinischen Eigenschaften die initiale Depressionsschwere ($p = 0,008$) und Alter ($p = 0,045$) als statistisch signifikante Moderatoren für die Depressionsschwere zum Post-Messzeitpunkt erwiesen, das heißt eine höhere anfängliche Depressionsschwere und höheres Alter führten zu geringeren depressiven Symptomen zum Post-Messzeitpunkt, wenn die Betroffenen an einer internetbasierten Intervention teilgenommen hatten. Begleitete Interventionen zeigten sich unbegleiteten Interventionen tendenziell überlegen. Dieser Unterschied wurde jedoch knapp nicht signifikant ($p = 0,057$).

Für welche TeilnehmerInnen mit MDD besteht das Risiko einer Symptomverschlechterung? (Studie 3)

In der zweiten IPD-MA (Studie 3) wurden 18 randomisiert-kontrollierte Studien mit insgesamt n = 2079 TeilnehmerInnen aufgenommen und mithilfe einer zweistufigen IPD-MA analysiert, in denen internetbasierte Interventionen zur Behandlung von Personen mit MDD mit Kontrollgruppen verglichen wurden. Für die oben genannte Fragestellung wurden verschiedene Subgruppenanalysen hinsichtlich eines möglichen Moderatorseffekts durchgeführt. Als Teilnehmereigenschaften sind Geschlecht, Alter, Bildung, komorbide Angststörung (ja / nein) und initiale Symptomschwere eingeflossen, während auf Studienebene die Verwendung eines diagnostischen Interviews (ja / nein), die Art der Rekrutierung (Allgemeinbevölkerung / klinisches Umfeld), die Art der Kontrollbedingung (aktiv / nicht aktiv) sowie das Risiko einer Verzerrung (niedrig / hoch) untersucht wurden. Darüber hinaus wurden moderierende Effekte durch die Art der Intervention betrachtet (theoretisches Modell der Intervention [CBT, andere] sowie Anzahl der Lektionen).

Das Bildungsniveau zeigte sich als einziger signifikanter Moderator für die Auswirkungen der Behandlung auf die Symptomverschlechterung, das heißt, dass für Teilnehmende mit einem niedrigeren Bildungsniveau im Vergleich zu einem höheren Bildungsniveau ein signifikant höheres Risiko für eine Verschlechterung bestand ($p = 0,03$). Alle anderen Unterschiede zwischen den Subgruppen bei den Verschlechterungsraten waren nicht signifikant ($p > 0,10$).

Hat vorangehende Psychotherapieerfahrung einen Einfluss auf den Behandlungserfolg für Personen mit MDD? (Studie 1)

Etwas mehr als die Hälfte der TeilnehmerInnen der randomisiert-kontrollierten Studie zur Evaluation des GET.ON Mood Enhancer-Programms (n = 77, 60,2 %) hatte bereits vor Beginn der Studienteilnahme wenigstens einmal psychotherapeutische Hilfe in Anspruch genommen. Der Anteil an TeilnehmerInnen mit Psychotherapieerfahrung war in der iCBT-Gruppe (n = 45, 69,2 %) deutlich höher als in der psychoedukativen Kontrollgruppe (n = 32, 48,5 %). Aufgrund dieser Ungleichgewichte in der Anzahl der TeilnehmerInnen mit einer Vorgeschichte der Psychotherapie zwischen den Studiengruppen wurde in dieser Studie ein zweiter

Analyseschritt durchgeführt, obwohl ursprünglich nicht vordergründig Moderatoren identifiziert werden sollten. Die Therapieerfahrung wurde ins Modell aufgenommen, indem ein fester Effekt für die Therapieerfahrung (ja / nein), der Zweifach-Interaktionsterm - Messzeitpunkt x Therapieerfahrung - und der Dreifach-Interaktionsterm - Messzeitpunkt x Gruppe x Therapieerfahrung ergänzt wurden.

Das angepasste Mixed-Effects-Model zeigte a) einen signifikanten Rückgang der Depressionsschwere von der Baseline bis zum Post-Messzeitpunkt (T1-T2) und von der Baseline bis zum Follow-Up (T1-T3) sowohl für iCBT als auch für OPE; und b) einen signifikant höheren Rückgang der Depressionsschwere nur bei den TeilnehmerInnen der OPE, die vor ihrem Eintritt in die aktuelle Studie eine Psychotherapie durchlaufen hatten, im Vergleich zu denen ohne Psychotherapieerfahrung (T1-T2 x Psychotherapieerfahrung / T1-T3 x Therapieerfahrung). Die Zweifach-Interaktion (T1-T2 x Gruppe) zeigte c) einen signifikant stärkeren Rückgang (-7,1 HRSD-Punkte) der Depressionsschwere von der Baseline bis T2 in der iCBT- verglichen mit der OPE-Gruppe unter TeilnehmerInnen ohne Psychotherapieerfahrung. Schließlich zeigte der signifikant positive Dreifach-Interaktionskoeffizient (T1-T2 x Psychotherapieerfahrung x Gruppe) an, dass d) beim Vergleich der Reduktion des Schweregrades der Depressionen von T1 bis T2 zwischen TeilnehmerInnen mit und ohne Psychotherapieerfahrung die mittlere T1-T2-Differenz bei den iCBT-Empfängern kleiner war als bei den OPE-Empfängern. Zusammenfassend lässt sich sagen, dass bei der MEM-Analyse, die an die Psychotherapieerfahrung angepasst wurde, kein Unterschied zwischen den beiden Behandlungsarmen in Bezug auf die Schwere der Depression (T1-T2) bei TeilnehmerInnen mit Psychotherapieerfahrung (d = 0,09, 95 % KI: -0,37 - 0,54) festgestellt wurde, aber ein signifikanter Gruppenunterschied bei denen ohne vorherige Psychotherapie beobachtet werden konnte. Dieser Effekt war groß (d = 0,82, 95 % KI: 0,25 - 1,40).

5.3 Nebenwirkungen von internetbasierten Maßnahmen

Kann die Teilnahme an internetbasierten Interventionen zur Behandlung von MDD zu einer signifikanten Symptomverschlechterung führen? (Studie 3 und Studie 1)

In Studie 3 wurden Verschlechterungs- und Rücklaufquoten nach dem weit verbreiteten reliablen Änderungsindex berechnet (RCI = reliable change index [131]). Teilnehmende, deren Ergebnisse von der Baseline bis zum Post-Messzeitpunkt RCIs unterhalb des Cutoff-Points von -1,96 aufwiesen, galten als verschlechtert.

Das Risiko für eine reliable Symptomverschlechterung von der Ausgangssituation bis zum Post-Messzeitpunkt war in der Interventionsgruppe signifikant geringer als in der Kontrollbedingung (RR 0,47, 95 % KI: 0,29 - 0,75) und das NNT zur Vermeidung einer zusätzlichen Verschlechterung betrug 43,21 (95 % KI: 25,83 - 132,10). Das Risiko einer Verschlechterung von der Baseline bis zum Follow-Up 1 (1 - 4 Monate) war in der Interventionsgruppe, verglichen mit der Kontrollgruppe, tendenziell geringer (RR 0,47, 95 % KI: 0,20 - 1,42), obwohl die Differenz keine statistische Signifikanz erreichte (p = 0,097). Es gab keine signifikanten Unterschiede zwischen den Gruppen hinsichtlich des relativen Risikos einer Verschlechterung von der Baseline bis zum Follow-Up 2 (p = 0,72).

In der randomisiert-kontrollierten Studie zur Evaluation des Programms GET.ON Mood Enhancer (Studie 1) wurde die Verschlechterung der depressiven Symptomatik im Laufe der Behandlung ebenfalls gemessen. Die TeilnehmerInnen wurden als "verschlechtert" eingestuft, wenn sie eine reliable negative Veränderung (-1,96) in der HRSD-24 gemäß RCI erlebten. Bei der Beurteilung der Anzahl der TeilnehmerInnen mit erhöhten Depressionswerten zur Baseline (≥ 4,42 Punkte im HRSD-24) erlebten sechs (9,2 %) und fünf (7,6 %) der Probanden in der iCBT- bzw. OPE-Gruppe eine reliable Verschlechterung von T1 bis T2. Diese Werte waren statistisch nicht unterschiedlich (χ^2 = 0,117, p = 0,732). Von T1 bis T3 zeigten drei (4,6 %) und sechs (9,1 %) Personen eine reliable Symptomverschlechterung, eine Differenz, die wiederum nicht statistisch signifikant war (χ^2 = 0,311, p = 0,492). Es gab keinen Zusammenhang zwischen den Verschlechterungsraten und der Adhärenz von T1 bis T2 (χ^2 = 1,520, p = 0,252) oder von T1 bis T3 (χ^2 = 2,135, p = 0,222). Es gab auch keinen Zusammenhang zwischen Verschlechterung und Studienabbruch von T1 bis T2 (χ^2 = 0,011, p = 1,000) oder von T1 bis T3 (χ^2 = 0,024, p = 1,000).

Kann die Teilnahme an einer internetbasierten Intervention zur Behandlung von MDD darüber hinaus zu weiteren unerwünschten Nebenwirkungen führen? (Studie 1)

Das erhöhte Suizidrisiko von Probanden während einer Studie ist ein weiterer potenzieller negativer Effekt. Im Rahmen des RCTs wurde eine klinisch signifikante Erhöhung der Punktzahl bei dem Suizid-Item des HRSD-24 von der Baseline bis zur Post-Messung oder zum 3-Monats-Follow-Up als Steigerung von mindestens 2 Punkten definiert (0 = „keine", 1 = „spürt, dass das Leben nicht lebenswert ist", 2 = „wünscht sich, dass er / sie tot wäre oder hat Gedanken an eine mögliche Selbsttötung", 3 = „suizidale Ideen, Gesten oder Pläne", 4 = „Selbstmordversuch"). Ein Wert von 3 oder 4 wurde als schweres Risiko angesehen. In den Gruppen iCBT und OPE berichteten vier (7,4 %) bzw. eine Person (1,9 %) von "Gedanken darüber, tot zu sein oder möglicherweise zu sterben" (Punktzahl = 2 beim Suizid-Item im HRSD-24) während der Woche vor dem Post-Messzeitpunkt. Zum 3-Monats-Follow-Up waren es vier (7,7 %) und vier (8,3 %). Im Vergleich zur Baseline blieb die Prävalenz der Selbstmordgedanken in beiden Gruppen stabil. Kein Teilnehmender einer der Behandlungsarme berichtete von selbstmörderischen Ideen, Gesten, Plänen oder Versuchen (HRSD-24 Suizid-Item Punktzahl = 3 oder 4).

Mögliche negative Auswirkungen auf die Einstellung zur Inanspruchnahme zukünftiger Therapieangebote (ATSPPH = Attitudes Toward Seeking Professional Psychological Help Scale [132]) wurden bei TeilnehmerInnen untersucht, die das a priori-Kriterium für eine positive Behandlungsreaktion nicht erreicht haben (iCBT: n = 46, 70,8 %; OPE: n = 50, 75,8 %). Die Einstellung zur zukünftigen Inanspruchnahme von therapeutischen Angeboten verbesserte sich in beiden Studiengruppen (iCBT: 0,28 Punkte; OPE: 0,33 Punkte), ohne signifikanten Unterschied zwischen den beiden Gruppen (T1-T2 x Gruppe, p = 0,321; d = 0,04; 95 % KI: -0,37 bis 0,46). Da die Effektgrößen positiv waren und die untere Grenze des Konfidenzintervalls für die vordefinierte Äquivalenzmarge von d = -0,20 nicht überschritten wurde, kann daraus geschlossen werden, dass es keine negativen Auswirkungen auf die Einstellung zur Suche nach psychologischer Hilfe bei denen gab, die auf die Intervention nicht reagierten.

Der modifizierte INEP (Inventory of Negative Effects in Psychotherapy [126]) wurde zur Messung anderer unerwünschter Ereignisse verwendet. Die in dieser Studie verwendete Version besteht aus 15 Items, die nach

allen negativen Effekten fragten, die Einzelpersonen während oder nach Abschluss des internetbasierten Trainingsprogramms erlitten, die dem Programm selbst zugeschrieben wurden, einschließlich a) negativer intrapersoneller Veränderungen; b) negativer Veränderungen in einer intimen Beziehung; c) negativer Auswirkungen auf Familie / Freunde; d) wahrgenommener Abhängigkeit von der psychotherapeutischen / psychotherapeutischen Intervention; und e) Stigmatisierung. Die Items wurden auf einer 7-Punkte-Likert-Skala bewertet, die von -3 (sehr negative Erfahrung) bis +3 (sehr positive Erfahrung) reicht, oder auf einer 4-Punkte-Likert-Skala, die von -3 (totale Übereinstimmung) bis 0 (überhaupt keine Übereinstimmung) reicht. Eine negative Antwort auf eine der Fragen zählte als unerwünschtes Ereignis. Bei T2 berichteten 17 der 65 Probanden (26,2 %) der iCBT-Gruppe über unerwünschte Nebenwirkungen, die sie der Teilnahme an der Intervention zuschrieben. Am häufigsten berichteten sie über Effekte im Bereich negativer intrapersoneller Veränderungen, mit den meisten Bewertungen zum Punkt "Während des Trainings oder seit Abschluss des Trainings gab es Phasen, in denen ich mich geistig unwohl fühlte." (n = 6, 9,2 %). Einige berichteten von wahrgenommener Stigmatisierung, Partnerschaftsproblemen, Problemen mit Familie oder Freunden oder von wahrgenommener Abhängigkeit vom eCoach. In der Kontrollgruppe kam der INEP-Fragebogen nicht zum Einsatz.

Kann die Teilnahme an internetbasierten Interventionen zur Behandlung von sD zu einer signifikanten Symptomverschlechterung führen? (Studie 2)

Im Rahmen der IPD-MA zur Evaluation internetbasierter Maßnahmen zur Behandlung von subklinischen Depressionen wurde eine potenzielle Symptomverschlechterung einerseits via RCI und andererseits als eine Zunahme der depressiven Ausgangssymptome um 50 % bis zum Post-Messzeitpunkt bestimmt. Zur Analyse wurden mehrstufige logistische Regressionsanalysen durchgeführt und Odds Ratios (OR) berechnet sowie die entsprechenden Anzahlen der zu behandelnden Fälle (NNTH = number needed to harm), um einen zusätzlichen Fall von Verschlechterung im Vergleich zur Kontrollgruppe zu erreichen.

Zum Post-Messzeitpunkt war das Risiko einer Verschlechterung basierend auf dem RCI in der Interventionsgruppe um 35 % (n = 54, 45,0 %) im Vergleich zur Kontrollgruppe (n = 81, 7,4 %) signifikant verringert (OR = 0,65; 95 % KI: 0,43 – 0,98, p = 0,038). Beim Follow-Up 2 (FU2) war es eine Reduzierung um 30 % (OR = 0,70; 95 % KI: 0,50 – 0,99, p = 0,046) in der Interventionsgruppe (n = 226, 20,8 %), verglichen mit der Kontrollgruppe (n = 277, 25,2%). Beim Follow-Up 1 (FU1) blieb das Risiko in der Interventionsgruppe (n = 72; 6,6 %) zwar geringer als in der Kontrollgruppe (n = 84; 7,7 %), aber der Unterschied war nicht statistisch signifikant (OR = 0,85; 95 % KI: 0,58 - 1,25, p = 0,412). Im Hinblick auf die NNTH war die internetbasierte Behandlung mit einem Fall von Symptomverschlechterung zum Post-Messzeitpunkt pro 41,43 (95 % KI: 22,58 – 250,08) TeilnehmerInnen verbunden, die eine Behandlung erhielten. Die NNTH für FU1 und FU2 waren NNTH = 96,84 (95 % KI: 31,35 – 10^6) bzw. NNTH = 22,44 (95 % KI: 12,53 – 107,20).

In der Interventionsgruppe wiesen zum Post-Messzeitpunkt n = 52 (4,8 %), zum FU1 n = 57 (5,2 %) und zum FU2 n = 187 (17,2 %) Teilnehmende einen Anstieg ihrer anfänglichen Symptome um mindestens 50 % auf. In der Kontrollgruppe war dies der Fall bei n = 63 (65,7 %), 66 (6,0 %) und 217 (19,8 %). Es gab keine signifikanten Unterschiede zwischen den Gruppen in den Verschlechterungsraten zum Post-Messzeitpunkt (OR = 0,82; 95 %

KI: 0,53 - 1,25, p = 0,345), FU1 (OR = 0,84; 95 % KI: 0,55 - 1,29, p = 0,419) und FU2 (OR = 0,82; 95 % KI: 0,58 – 1,15, p = 0,242). Die internetbasierte Intervention war mit einem Fall von 50 % Symptomanstieg zum Post-Messzeitpunkt pro 104,35 (95 % KI: 33,35 - 10^6) TeilnehmerInnen verbunden, die eine Behandlung erhielten. Die NNTH für FU1 und FU2 waren NNTH = 129,54 (95 % KI: 36,99 – 10^6) bzw. NNTH = 38,82 (95 % KI: 17,06 - 10^6).

6. Zusammenfassende Diskussion

6.1 Effektivität internetbasierter Maßnahmen für Personen mit depressiven Symptomen

In zahlreichen Studien und Meta-Analysen konnte bereits gezeigt werden, dass internetbasierte Interventionen sowohl für Personen mit majorer Depression als auch mit subklinischen Depressionen effektiv sind. Im Rahmen dieses Dissertationsvorhabens ließen sich noch weitere Wissenslücken schließen:

Die Ergebnisse des RCTs in Studie 1 zeigten, dass internetbasierte Interventionen für Personen mit mittelschweren bis starken depressiven Symptomen auch dann effektiv sind, wenn man sie mit einer aktiven Kontrollbedingung (Online-Psychoedukation) vergleicht. Es ließen sich große Effekte innerhalb der Interventionsgruppe für die Symptomveränderung zwischen der Vorher- und der Nachher-Messung von Cohen's d = 1,10 feststellen. Auch die Veränderung von der Vorher-Messung bis zum 3-Monats-Follow-Up zeigt einen großen Effekt von d = 1,01. Diese Ergebnisse stimmen mit denen einer aktuellen Meta-Analyse über internet- und mobilbasierte Depressionsinterventionen für Menschen mit diagnostizierter Depression überein [61]. Darüber hinaus stimmen sie auch mit den Ergebnissen früherer Studien überein, die innerhalb des Inkubator-Projekts der Leuphana Universität Lüneburg mit anderen (nicht verkürzten) Versionen von GET.ON Mood Enhancer durchgeführt wurden: Hier ließen sich vergleichbare Effekte für Personen mit subklinischen Depressionen (d = 1,06 [71]) und noch höhere Effekte für Patienten mit Diabetes mellitus und komorbider Depression (d = 1,40 [69]) finden. Für die OPE-Bedingung wurde im Vorfeld ebenfalls ein signifikanter Effekt erwartet. Frühere Untersuchungen zeigten Ergebnisse von d = 0,29 bis 0,65. Der gefundene Prä-Post-Effekt (d = 0,60) fällt zwar in das zu erwartende Spektrum, der Effekt von der Vorher-Messung bis zum 3-Monats-Follow-Up war jedoch überraschend hoch (d = 0,87). Dieses Ergebnis ist sogar höher als in Studien unserer eigenen Forschungsgruppe, die dieselbe Online-Psychoeduktionsintervention verwendeten [69,71,133].

Der Zwischen-Gruppen-Effekt fiel hier im Vergleich zu früheren Studien [69,71,134] unerwartet klein aus, was sich möglicherweise durch die auffallend hohe Chronizität der TeilnehmerInnen oder durch die ungleiche Verteilung der Teilnehmenden mit Psychotherapieerfahrung auf die beiden Gruppen erklären lässt (vgl. Abschnitt 6.2). Interessanterweise zeigten die hier festgestellten Mittelwerte einen stabilen Effekt für iCBT zwischen dem Post-Messzeitpunkt und dem Follow-Up, während die Psychoedukation zunächst eine geringere Verbesserung zeigte, aber weiterhin einen positiven Einfluss auf die Schwere der Depression vom Post-Messzeitpunkt bis zum Follow-Up hatte. Diese Ergebnisse deuten darauf hin, dass beide Arten von Interventionen die Schwere der Depression reduzieren können, aber iCBT möglicherweise schneller als Psychoedukation wirkt.

Der hier betrachtete Gruppenvergleich fand mit einer Kontrollgruppe statt, die über eine reine Wartekontrollgruppe hinausgeht. Gründe hierfür wurden in Abschnitt 3.1 erläutert. Die Wahl der Kontrollbedingung spielt eine erhebliche Rolle für die Interpretation der Ergebnisse. Welche Art von

Kontrollbedingung sich für verschiedene Studiendesigns eignet, wurde in der Vergangenheit bereits viel diskutiert [135,136]. Während in der Medizin ein Medikamenten-Placebo gleich eine Vielzahl von Aufgaben erfüllt (Regression zur Mitte, natürlicher Krankheitsverlauf, Hawthorne-Effekt, Placebo-Effekt…), ist es in der Psychologie eine größere Herausforderung, eine psychologische Placebo-Bedingung einzusetzen [137]. Aus diesem Grund greifen viele Studien-Designs auf Routineversorgung (TAU), Nicht-Behandlung oder Wartelisten zurück. In einer Netzwerk-Meta-Analyse mit 49 randomisiert-kontrollierten Studien zur Face-to-Face-Behandlung von Personen mit depressiver Symptomatik wurde die Versuchsbedingung mit den verschiedenen Kontrollbedingungen Nicht-Behandlung, Warteliste und psychologisches Placebo verglichen. Die berechneten Effektstärken für die Behandlung auf Basis der Kognitiven Verhaltenstherapie (KVT) waren je nach Kontrollbedingung verschieden. Das Odds Ratio (OR) für eine positive Behandlungsreaktion (definiert als Reduzierung der depressiven Symptome um mindestens 50 %) war mit 1,7 beim Vergleich von KVT mit einem psychologischen Placebo statistisch nicht signifikant. Eine Signifikanz ließ sich jedoch im Vergleich von KVT mit einer Nicht-Behandlung (OR = 2,4) und im Vergleich zur Warteliste (OR = 6,3) nachweisen. Es zeigte sich, dass die Nicht-Behandlung sogar der Wartelistenbedingung überlegen ist (OR = 2,9) [137]. Allerdings sind diese Ergebnisse mit Vorsicht zu interpretieren, da nicht alle eingeschlossenen Studien eine hohe Qualität aufwiesen, gemessen mit dem Cochrane Collaboration „Risk-of-Bias-Instrument“ [138]. Darüber hinaus zeigte sich der Vorteil der Nicht-Behandlung gegenüber der Wartelisten-Bedingung in einer Sensitivitätsanalyse, die die Verzerrung der Effekte von Studien mit geringem Stichprobenumfang berücksichtigt hat, als nicht mehr signifikant [137]. Auch wenn die StudienteilnehmerInnen in allen Bedingungen, so auch in denen der Nicht-Behandlung oder Warteliste meist die Erlaubnis haben, während der Studienphase medizinische Hilfeleistungen ihrer Wahl in Anspruch zu nehmen, ist es ethisch in Anbetracht ihres Leidensdrucks fragwürdig, ihnen durch den Einsatz einer Nicht-Behandlungs-Bedingung eine Behandlung vorzuenthalten, die aus evidenzbasierten Bausteinen der Kognitiven Verhaltenstherapie besteht. Dies erscheint nicht vereinbar mit der „Declaration of Helsinki“. Dort wird zu besonderer Sorgfalt bei der Wahl der Kontrollbedingung aufgerufen: Ein Placebo oder eine Nicht-Behandlung sollen nur beim Vorliegen von zwingenden und wissenschaftlich fundierten Gründen eingesetzt werden [139].

Die Ergebnisse der IPD-MA in Studie 2 bestätigen die Wirksamkeit von internetbasierten Maßnahmen für Personen mit subklinischen Symptomen, verglichen mit Wartelisten oder Routineversorgung. Anders als in bisherigen Meta-Analysen basieren diese Ergebnisse auf den Rohdaten der jeweiligen StudienteilnehmerInnen. Die Zwischen-Gruppen-Effekte fielen etwas höher aus als bisher in der Literatur berichtet [63,64,73]. Ein Grund für die höheren Effekte könnte darüber hinaus in der Flexibilität von internetbasierten Interventionen und der Möglichkeiten liegen, die TeilnehmerInnen direkt in ihrem Alltag zu unterstützen, so dass es ihnen häufiger gelingt, notwendige Verhaltensänderungen in ihre Routinen zu integrieren und diese aufrechtzuerhalten als es z.B. bei traditionellen gruppenbasierten Präventivmaßnahmen der Fall ist, die das am häufigsten eingesetzte Format für die Depressionsprävention darstellen [50]. Allerdings sind zukünftige Untersuchungen erforderlich, um solche Annahmen zu bestätigen. Die Reduzierung des Risikos, eine majore Depression zu entwickeln, fiel entsprechend einer vorigen Meta-Analyse [50] aus.

Diese und auch vorangehende Ergebnisse zeigen das hohe Potenzial von internetbasierten Interventionen und so ist es nicht verwunderlich, dass das Interesse an eMental-Health im Allgemeinen und an internetbasierten Interventionen im Speziellen in den vergangenen Jahren immens angewachsen ist und derartige Maßnahmen im Bereich der psychischen Gesundheit zunehmend häufiger zum Einsatz kommen. Dies liegt in erster Linie an dem großen Potenzial, Kosten einzusparen bei gleichzeitig hohen zu erwartenden Effekten [140]. Es ist jedoch zu beachten und zeigt sich bereits als Resultat mancher Implementierungsversuche, dass Studienergebnisse häufig nicht eins zu eins auf die tatsächlichen Bedingungen der Routineversorgung übertragbar sind. Die Bedingungen einer randomisiert-kontrollierten Studie sind hoch strukturiert und beinhalten meist eine proaktive Teilnehmerrekrutierung, menschlichen Kontakt mit den Versuchsleitern und vorab bereits festgelegte Messzeitpunkte, an denen Fragebogen beantwortet oder diagnostische Interviews geführt werden. Diese Strukturierung führt zu einer erhöhten Aufmerksamkeit bei den TeilnehmerInnen und kann einen substanziellen Einfluss darauf haben, wie stark StudienteilnehmerInnen sich innerhalb der Intervention engagieren, wodurch die Effekte für internetbasierte Selbsthilfeinterventionen im Vergleich zu Angeboten in der Routineversorgung überschätzt und gleichzeitig die Generalisierbarkeit der Ergebnisse eingeschränkt werden können [140–142]. Diese Annahme wird gestützt von Studien, in denen die Implementierung internetbasierter Maßnahmen in die Praxis nicht geglückt ist [143,144]. Es ist also denkbar, dass sowohl die Adhärenz als auch die Effektivität geringer sind, wenn die Sicherstellung des Teilnehmerengagements außerhalb randomisiert-kontrollierter Studien wegfällt. Eine solche Annahme wird durch pragmatische Studien gestützt, in denen kein zusätzlicher Nutzen von unbegleiteten Selbsthilfeprogrammen im Vergleich zur Routineversorgung festgestellt wurde [145]. Dies bestätigt auch eine jüngst veröffentlichte Studie, die jeweils das gemessene Nutzerverhalten in der studienbasierten Forschung mit der Nutzung derselben unbegleiteten internetbasierten Interventionen für psychische Gesundheit verglich. Es flossen 11 Vergleiche in die Analyse ein, in denen Studien aktiv ihre TeilnehmerInnen rekrutierten und Vorher-Nachher-Messungen durchführten, um sie dann mit der realen Nutzung desselben Programms zu vergleichen. Die mediane Programmnutzungsrate im Studien-Setting war 4,06-mal höher als die reale Nutzung desselben Programms. Der Schweregrad der klinischen Symptome, ob Selbsteinschätzung oder Fremdbewertung zum Einsatz kamen, das Studiendesign und die Programmkosten hatten keinen Einfluss auf diese Unterschiede [142]. Diese Erkenntnisse sind nicht überraschend oder ungewöhnlich, sondern zeigen sich generell in klinischen Studien [146,147]. Dennoch sollten sie bei der zukünftigen Implementierung internetbasierter Maßnahmen bedacht werden. Schätzungsweise müssen höhere Anstrengungen als in Studien unternommen werden, die TeilnehmerInnen zu erreichen und zu motivieren, die Trainings vollständig zu durchlaufen, um einen mit den Studien vergleichbaren Effekt auch in der Routineversorgung erzielen zu können.

6.2 Faktoren für den Behandlungserfolg internetbasierter Maßnahmen

Wie in Abschnitt 3.2 beschrieben, ist die Fragestellung, welche Faktoren den Behandlungserfolg moderieren, in der bisherigen Forschung noch nicht ausreichend beantwortet. Die zumeist inkonsistenten Studienergebnisse weisen darauf hin, dass es sich in manchen Fällen vielleicht eher um Zufalls- als um gesicherte Befunde handelt. Meta-Analysen, die auf Basis der Rohdaten aller StudienteilnehmerInnen durchgeführt werden, haben

gegenüber traditionellen Meta-Analysen und Einzelstudien den Vorteil, dass sie deutlich mehr statistische Power haben, um Moderatoreffekte zu identifizieren. In der IPD-MA (Studie 2) wäre es wünschenswert gewesen, das Signifikanzniveau bei den Moderatoranalysen entsprechend der Anzahl der getesteten Variablen anzupassen, um das Risiko für Zufallsbefunde zu reduzieren. Dies wurde versäumt, so dass ein erhöhter Fehler 1. Art vorliegt, d.h. möglicherweise zeigen sich Moderatoren als signifikant, die es tatsächlich nicht sind. Gleichzeitig werden mögliche moderierende Effekte eventuell nicht identifiziert, weil der Stichprobenumfang für sehr kleine Effekte noch immer zu gering ist. Aus diesem Grund sollen die hier gefundenen Ergebnisse mit Vorsicht diskutiert und interpretiert werden und ggf. eher als hypothesengenerierend für weitere Forschung in Betracht gezogen werden.

Das Maß der Begleitung der TeilnehmerInnen durch eine fachlich qualifizierte Person ist eine der wenigen Variablen, über die bisher im Bereich der Forschung zu internetbasierten Interventionen zur Behandlung von Depressionen oder depressiver Symptomatik weitestgehend Einigkeit besteht. Mehrere Meta-Analysen zu internetbasierten Interventionen zur Behandlung von majoren Depressionen [62,96,97] sowie auch die hier vorgestellte IPD-MA für Teilnehmende mit subklinischen Symptomen (Studie 2) zeigten, dass begleitete Internet-Interventionen generell zu besseren Effekten hinsichtlich der depressiven Symptomatik führen als unbegleitete Interventionen, so dass es augenscheinlich Sinn macht, diese Formate bevorzugt einzusetzen, unter anderem auch weil die Begleitung durch einen Psychotherapeuten oder eine geschulte Person als adhärenzfördernde Maßnahme betrachtet werden kann [148,149]. Obwohl die internetbasierten Interventionen nachweislich effektiv in der Reduzierung depressiver Symptome sind, brechen viele Teilnehmende die Benutzung früher oder später wieder ab [97,150]. Offenbar führt die Begleitung der TeilnehmerInnen neben einer besseren Effektivität auch zu einer erhöhten Motivation, zu mehr Zeit, die mit der Intervention verbracht wird [151] und zu einer höheren Anzahl abgeschlossener Lektionen [152]. Die Begleitung durch einen eCoach oder Online-Therapeuten erfordert jedoch die Festlegung, wie diese Begleitung aussehen sollte, um den Nutzen der Intervention zu maximieren. Es könnte in Anbetracht der Kosteneffektivität zielführend sein, die Fragen der Intensität und der Art der Begleitung zu beantworten, um ein optimales Kosten-Nutzen-Verhältnis zu erzielen. Für die Art der Begleitung wurden bereits vergleichende Studien durchgeführt (z.B. [153]), aber die Ergebnislage ist weiterhin unklar [154]. Vermutlich gibt es neben den individuellen Bedürfnissen der TeilnehmerInnen noch weitere motivationale oder volitionale Einflussfaktoren, die eine Begleitung mehr oder weniger erfolgversprechend machen. Im „Efficiency Model“ von Schueller et al. wird Effizienz als das Verhältnis von Nutzen und Ressourcen definiert. Wenn das Verhältnis zwischen Ressourcen und Nutzen linear ist, dann sollte die Frage, ob mehr Unterstützung geleistet werden soll, auf der Grundlage der verfügbaren Ressourcen und des gewünschten Ergebnisses gestellt werden. Oft ist dieses Verhältnis jedoch nicht linear, weil es zwischen dem Benutzer und der Intervention zu Unstimmigkeiten kommt. Anstatt den Fokus auf die unzähligen möglichen Wirkmechanismen zu legen, konzentrieren die Autoren sich stattdessen auf fünf kritische Fehlerpunkte, die bei der Begleitung als ursächlich für die Adhärenz angesehen werden: Usability (technische Barrieren), Engagement (fehlende Motivation, Intention oder nicht-motivierende Darstellung der Inhalte), Passung (fehlende Übereinstimmung der Inhalte der Intervention mit den Bedürfnissen des Betroffenen), Wissen (fehlendes Verstehen oder falsche Anwendung der Inhalte) und

Umsetzung (Anwendung im Alltag gelingt nicht) [155]. Die in dieser Arbeit identifizierten Moderatoren sollen unter Berücksichtigung dieses Modells betrachtet werden.

Bei der Auswertung der Daten der IPD-MA für TeilnehmerInnen mit subklinischen Symptomen (Studie 2) zeigte sich, dass eine hohe initiale Symptomschwere für die InterventionsteilnehmerInnen zu einem niedrigeren Depressionswert zum Post-Messzeitpunkt führt. Frühere Einzelstudien zeigten entweder, dass StudienteilnehmerInnen mit niedrigen Anfangssymptomen besser von Präventionsmaßnahmen profitieren [156], während andere Studien den gegenteiligen Effekt oder zumindest einen Trend in diese Richtung [157–159] und mehrere Studien überhaupt keinen moderierenden Effekt fanden (z.B. [87,160,161]). Sowohl majore als auch subklinische Depressionen gehen häufig mit Antriebslosigkeit, Interessenverlust und Konzentrationsproblemen einher [1]. Dies hat unter Umständen einen erheblichen Einfluss auf die Motivation und Intention, an einer internetbasierten Intervention teilzunehmen (Engagement), ihre Inhalte im Alltag umzusetzen (Umsetzung) oder mit technischen Barrieren umzugehen (Usability). Insbesondere für Personen mit hoher initialer Symptomschwere erscheint es hierbei besonders relevant, dass die Interventionen möglichst niedrigschwellig und ansprechend gestaltet sind, vorher ausgiebig hinsichtlich ihrer Usability getestet werden und sich idealerweise auch an die psychotherapeutische Vorgeschichte der Betroffenen anpassen ließen, beispielsweise durch mehr Wahlmöglichkeiten bezüglich der Inhalte. Dies könnte einerseits helfen, unnötige Wiederholungen zu vermeiden und andererseits sicherzustellen, dass wesentliche Themen nicht unbeachtet bleiben. So könnte der Teilnehmende Zugriff auf die Inhalte bekommen, die für ihn relevant sind (Passung) und möglichst effizient behandelt werden: Während für Therapie-Neulinge die Behandlung der Symptome vordergründig sein könnte, könnte für Personen, die bereits Therapieerfahrung haben, der Fokus auf Rückfallprophylaxe im Vordergrund stehen.

Ebenfalls in Studie 2 zeigte sich, dass Teilnehmende mit höherem Alter stärker profitierten, wenn sie an einer internetbasierten Intervention teilgenommen hatten. Dies wurde auch in einer aktuellen Meta-Analyse auf Basis individueller Teilnehmerdaten (IPD-MA) zur internetbasierten Behandlung von MDD gefunden [84]. Im Bereich der subklinischen Depression führten mehrere Einzelstudien zu gemischten Ergebnissen: Vázquez et al. [87] zeigten beispielsweise, dass jüngere Krankenpflegerinnen mehr von dem internetbasierten kognitiven Verhaltenstherapieprogramm (iCBT) profitierten als ältere, während sich das Alter in einer Studie von Button et al. [93] beim Vergleich von iCBT versus Routineversorgung nicht als signifikanter Moderator für den Behandlungserfolg erwies.

Es zeigte sich lediglich ein Trend, dass begleitete Programme im Vergleich zu reinen Selbsthilfemaßnahmen zu größeren Behandlungserfolgen führten. Es gibt bisher keine weiteren Meta-Analysen oder Reviews, die Begleitung als Moderator in Internet-Interventionen für subklinische Depressionen untersuchen, aber eine andere Einzelstudie fand, dass halbstandardisierte Begleitung bei einem iCBT-Programm für leichte bis mittelschwere Depressionen zwar hinsichtlich der depressiven Symptomatik nicht effektiver war als standardisiertes Feedback, jedoch zu höheren Abbruchraten führte [162]. Im Bereich der majoren Depression zeigten zahlreiche Meta-Analysen der letzten Jahren eine Überlegenheit von begleiteten Interventionen im Vergleich zu unbegleiteten [62,96,97]. Darüber hinaus wurden keine weiteren Moderatoren identifiziert.

Die durchgeführte randomisiert-kontrollierte Studie (Studie 1) zeigte überraschende Ergebnisse für Personen mit MDD hinsichtlich ihrer Psychotherapieerfahrung: Aufgrund der Tatsache, dass Personen mit vorangehender Psychotherapieerfahrung, die einen erheblichen Anteil der Stichprobe ausmachten, ungleichmäßig auf die beiden Studiengruppen verteilt waren, wurde diese Variable in einem weiteren Analyseschritt ins Modell eingeschlossen, um einen möglichen moderierenden Effekt zu untersuchen. Im Rahmen der Analyse ließ sich feststellen, dass iCBT der Online-Psychoedukation hinsichtlich einer Reduzierung der Symptomschwere offenbar nur überlegen ist, wenn diese Personen zuvor noch keine Psychotherapieerfahrung gesammelt haben, oder anders formuliert: Es zeigte sich, dass für Personen mit MDD, die bereits Psychotherapieerfahrung mitbringen, eine kurze psychoedukative Einheit dieselben Erfolge bringt wie das Durchlaufen des gesamten Programms, während Personen ohne Vorerfahrung nicht von der Psychoedukation, dafür aber erheblich von dem intensiven Programm profitierten. Jedes betroffene Individuum bringt eine eigene Geschichte und auch Behandlungshistorie mit sich. Es ist denkbar, dass internetbasierte Maßnahmen besonders hilfreich sind, wenn sie die erste Hilfe darstellen, die Personen mit MDD in Anspruch nehmen, da sie spezifische therapeutische Strategien enthalten, die ihnen einen neuen Weg zur Bewältigung ihrer Probleme bieten können. Psychoedukation könnte hingegen eine Art Auffrischung für diejenigen darstellen, die bereits Erfahrung mit psychotherapeutischen Maßnahmen haben. Es wird dabei an zuvor erlerntes Wissen und Bewältigungsverhalten angeknüpft. Für diese Personen würde eine intensivere internetbasierte Maßnahme über den psychoedukativen Auffrischungskurs keinen entscheidenden Zusatznutzen bringen. Wenn die Psychotherapieerfahrung bei der Zusammenstellung der Programminhalte Berücksichtigung fände, könnte dies zu einer besseren Passung und demnach auch zu einem höheren Engagement führen.

Im Rahmen der zweiten IPD-MA (Studie 3) konnte das Bildungsniveau als signifikanter Moderator für den Behandlungserfolg identifiziert werden, wobei wenig gebildete Teilnehmende ein größeres Risiko für eine Symptomverschlechterung aufweisen als hoch gebildete Teilnehmende. Dieser Befund entspricht den Ergebnissen mehrerer randomisiert-kontrollierter Studien, die ebenfalls zeigten, dass ein niedrigerer Bildungsgrad bei internetbasierten Selbsthilfeinterventionen mit schlechteren Behandlungsergebnissen verbunden ist [106,163]. Gleichzeitig wiesen die Ergebnisse einer anderen IPD-MA mit dem gleichen Datensatz aus Studie 3 darauf hin, dass das Bildungsniveau sich andersherum nicht als Prädiktor für einen Behandlungserfolg herausstellte [84]. Eine Erklärung für solche Befunde kann sein, dass Patienten mit einem niedrigeren Bildungsniveau Schwierigkeiten beim Verständnis der Behandlungsinhalte haben, da die meisten Selbsthilfe-Maßnahmen ein recht fortgeschrittenes Leseverständnis erfordern (Wissen). Dadurch können die eigentlich effektiven Werkzeuge nicht angemessen genutzt werden. Das wiederum kann die Selbstwirksamkeit der TeilnehmerInnen verringern und Gefühle der Hoffnungslosigkeit erzeugen. Obwohl alle in die IPD-MA eingeschlossenen Studien eine Form der Begleitung beinhalteten, könnte diese Art der Unterstützung für einige Personen nicht ausreichend sein, um die Barriere der niedrigen Bildung zu überwinden. Eine intensivere Maßnahme, wie z.B. die persönliche Begegnung mit einem Therapeuten, könnte diesen Patienten möglicherweise helfen, die Behandlungsinhalte besser zu verstehen, was hypothetisch zu einem geringeren Risiko der Symptomverschlechterung führt [164]. Auch wären möglicherweise andere, weniger kognitiv ausgerichtete Therapieansätze für diese Personen hilfreicher. Um zu mehr Klarheit diesbezüglich zu gelangen,

wären Vergleichsstudien aufschlussreich, die Programme evaluieren, bei denen das Bildungsniveau auf unterschiedliche Art berücksichtigt oder künstlich manipuliert wird, beispielsweise durch das Sprachniveau, die Art der Darstellung (weniger Text, mehr visuelle Erklärungen, zusätzliche Erläuterungen, geringerer Programmumfang, intensivere Begleitung…). Darüber hinaus wären weitere Studien wünschenswert, die untersuchen, ob Teilnehmende mit einem hohen Risiko für eine Symptomverschlechterung stärker von einer Face-to-Face-Therapie oder einem anderen therapeutischen Ansatz profitieren würden. Falls dies nicht der Fall sein sollte und internetbasierte Interventionen gleich gute oder gar bessere Behandlungserfolge erzielen würden, macht es Sinn, zu überlegen, wie diese Gruppe gezielt erreicht werden kann. In bisherigen Studien zeigte sich, dass Personen mit niedriger Bildung unter den TeilnehmerInnen häufig unterrepräsentiert sind (z.B. [84]).

Ein weiterer relevanter Aspekt, der bisher in der Forschung nur wenig Beachtung fand, ist die Tatsache, wie beispielsweise anhand vieler Meta-Analysen festzustellen, dass die meisten Maßnahmen für Depressionen, die bisher online umgesetzt wurden, auf den Annahmen und Kernelementen der Kognitiven Verhaltenstherapie basieren [61,165–167]. Die KVT eignet sich augenscheinlich sehr gut dafür, die Themenschwerpunkte als interaktive Selbsthilfemaßnahme digital umzusetzen. Andere Therapieformen wurden in ihrer digitalen Umsetzung bisher nur in vergleichsweise wenigen Studien untersucht, z.B. die psychodynamische Therapie [168], Achtsamkeit [169,170], Akzeptanz- und Commitment-Therapie [171], Modifikation des kognitiven Bias [172], Problemlösen [173,174], Verhaltensaktivierung [175] oder körperliche Aktivität [176]. Darüber hinaus gibt es im Bereich der internetbasierten Maßnahmen nur sehr wenige Vergleichsstudien, die verschiedene Therapieschulen hinsichtlich ihrer Effektivität miteinander vergleichen (z.B. [175]). Dabei ist zu beachten, dass nicht jede Therapieform für alle psychischen Erkrankungen geeignet ist, das heißt in vielen Fällen bekommen Betroffene nicht die Therapie, von der sie am besten profitieren würden (Passung). Auch die Bildung spielt bei diesem Aspekt sicher eine nicht unwesentliche Rolle, denn je nach therapeutischem Ansatz können die kognitiven Anforderungen und die Erfordernis eines tieferen Verständnisses mehr oder weniger bedeutsam sein. Idealerweise sollte es eine rationale Entscheidungsgrundlage geben, gestaffelt nach Chancen und Aufwand, um den bestmöglichen Behandlungserfolg zu erzielen.

So erfolgversprechend und effektiv internetbasierte Maßnahmen sich in Studien zur Behandlung von depressiver Symptomatik erwiesen haben, so unflexibel und starr sind sie bisher noch in ihren Inhalten und in ihrem Aufbau. Zwar stellt die standardisierte Behandlung via Internet eine kosteneffektive und gut skalierbare Behandlungsalternative dar, dennoch kann es passieren, dass für eine Vielzahl von Individuen die Behandlung nicht ausreichend gut ist, um ihre spezielle Situation und Bedürfnislage zu berücksichtigen. Im Face-to-Face-Kontakt erscheint dies auf den ersten Blick erheblich einfacher, da der behandelnde Therapeut sich jeweils auf seinen Klienten einstellen kann – je nach Vorgeschichte, Bildungsniveau oder Bedürfnislage. An dieser Stelle zeigen internetbasierte Maßnahmen Verbesserungspotenzial und eine Individualisierung der Inhalte erscheint unter diesem Aspekt als notwendig und sinnvoll. Dafür ist weitere Forschung hinsichtlich internetbasierter individualisierter Psychotherapie erforderlich.

6.3 Nebenwirkungen von internetbasierten Maßnahmen

Neben den erfolgversprechenden Eigenschaften von internetbasierten Interventionen dürfen auch mögliche Nebeneffekte nicht außer Acht gelassen werden. Es erscheint plausibel, dass Patienten während ihrer Behandlung aufgrund von majoren Depressionen oder subklinischen depressiven Symptomen eine mögliche Verschlechterung ihrer Symptome erleben. Eine Erklärung für die verminderte Stimmung während der Behandlung könnte zum Beispiel sein, dass KVT-basierte Expositionsübungen unangenehme Gedanken und Emotionen hervorrufen können, die sich gegebenenfalls negativ auf die Stimmung einer Person auswirken. Ein solcher negativer Nebeneffekt wie Stimmungsschwankungen könnte als ein normales Phänomen im Laufe einer psychologischen Intervention angesehen werden [177]. Auch führt die Veränderung von dysfunktionalen Verhaltensmustern unter Umständen zu Problemen mit den Mitmenschen, die diese Veränderung zunächst nicht nachvollziehen können oder weil diese Mitmenschen einen negativen Einfluss auf die StudienteilnehmerInnen hatten und diese sich nun von ihnen lösen. Diese Erkenntnisse sind nicht neu, sondern zeigten sich bereits in den ersten Jahren der Psychotherapieforschung [120,121]. Unkontrollierte Studien ergaben einen Anteil von Symptomverschlechterungen von 3 bis 14 % bei Psychotherapie im Allgemeinen [116–119].

Im Zuge dieser Dissertation wurden die Verschlechterungsraten von StudienteilnehmerInnen mit depressiver Symptomatik in vielfältiger Hinsicht untersucht. Die Ergebnisse sind jedoch inkonsistent: Die IPD-MA für Personen mit MDD (Studie 3) hatte die reliable Symptomverschlechterung als primären Endpunkt. Die Ergebnisse dieser Untersuchung deuten darauf hin, dass die Teilnahme an internetbasierten Selbsthilfeprogrammen mit einem geringeren Risiko einer Symptomverschlechterung (RR 0,47) im Vergleich zur Kontrollgruppe verbunden ist.

Dieses Ergebnis zeigte sich nicht in der randomisiert-kontrollierten Studie für Personen mit MDD (Studie 1). Hier gab es keinen signifikanten Gruppenunterschied hinsichtlich einer reliablen Symptomverschlechterung, allerdings ist zu bedenken, dass hier zwei aktive Versuchsbedingungen in einer verhältnismäßig kleinen Stichprobe untersucht wurden, deren Umfang sich bei der Studienplanung an einem anderen Zielkriterium orientierte.

Die IPD-MA zur Evaluation internetbasierter Interventionen zur Behandlung subklinischer Depressionen (Studie 2) zeigte einen signifikanten Gruppenunterschied hinsichtlich einer reliablen Symptomverschlechterung zugunsten der Interventionsgruppe, verglichen mit der Kontrollgruppe, zum Post-Messzeitpunkt sowie zum 12-Monats-Follow-Up. Das Risiko einer reliablen Symptomverschlechterung in der Interventionsgruppe im Vergleich zur Kontrollgruppe ließ sich zum Post-Messzeitpunkt um 35 % (OR = 0,65) und zum FU2 um 30 % (OR = 70,0) reduzieren, was sich mit den Ergebnissen aus Studie 3 in Einklang bringen lässt.

Neben einer möglichen Symptomverschlechterung wurden in Studie 1 noch weitere Nebenwirkungen ausgewertet: Die Subgruppenanalyse der TeilnehmerInnen, die das Kriterium für eine positive Behandlungsreaktion nicht erreicht haben, ergab keinen Unterschied in der Einstellung oder Veränderung der Einstellung zur Suche nach professioneller psychologischer Hilfe zwischen den TeilnehmerInnen der

internetbasierten Intervention GET.ON Mood Enhancer und der Psychoedukations-Bedingung. Dies entspricht den Ergebnissen andere Untersuchungen, die die Auswirkungen von iCBT auf die Einstellung zur Hilfesuche evaluiert haben, was darauf hindeutet, dass selbst wenn jemand nicht auf iCBT reagiert, dies seine Entscheidung, in Zukunft andere Hilfsquellen zu suchen, nicht zu beeinträchtigen scheint [35]. Hinsichtlich der Suizidalität konnten keine Fälle von schweren Selbstmordgedanken festgestellt werden und die Suizidalitäts-Prävalenz blieb in beiden Gruppen zwischen den Messzeitpunkten stabil. Siebzehn Probanden (26 %) in der iCBT-Gruppe führten Anzeichen von anderen negativen Effekten, gemessen mit dem modifizierten INEP (The Inventory of Negative Effects in Psychotherapy [126]), direkt auf die Intervention zurück. Der in der vorliegenden Studie am häufigsten berichtete Nebeneffekt war eine verminderte Stimmung während der Interventionsphase. Diese Nebenwirkungen, z.B. dass es den TeilnehmerInnen während der Behandlung schlechter ging oder es zu Problemen in zwischenmenschlichen Beziehungen kam, hatte augenscheinlich jedoch keinen Einfluss auf das Behandlungsergebnis. Es ist hierbei wichtig zu bedenken, dass jedwede negative Reaktion auf eine der 15 INEP-Aussagen als unerwünschtes Ereignis eingestuft wurde und dementsprechend mit gleicher Gewichtung in den Summenwert einfloss, unabhängig von Inhalt des Items und Intensität der Item-Antwort. Daher können die aus dieser Maßnahme resultierenden negativen Nebenwirkungen überschätzt werden. Darüber hinaus kam der INEP-Fragebogen in der Kontrollgruppe nicht zum Einsatz, weil die Items inhaltlich nicht stimmig für die Kontrollbedingung der Online-Psychoedukation erschienen. So konnte kein statistischer Vergleich zwischen den beiden Gruppen angestellt werden. In einer aktuellen Studie, die ein vergleichbares internetbasiertes Programm zur Behandlung von Depressionen mit einem 6-wöchigen Training zur progressiven Muskelentspannung vergleicht, wird der INEP in beiden Gruppen verwendet. Es zeigen sich keine statistisch signifikanten Unterschiede zwischen der Interventions- und der Kontrollgruppe, weder in der Anzahl der Items noch in der Anzahl der Personen, die negative Effekte berichten [178]. Darüber hinaus sind die Ergebnisse vergleichbar mit den Zahlen in Studie 1.

Hier zeigt sich deutlich der Handlungsbedarf in der aktuellen Forschung zu internetbasierten Interventionen, indem ein Konsens gefunden werden sollte, wie Nebeneffekte gemessen und berichtet werden sollten. Rozental et al. empfehlen hierzu in ihrem „Consensus Statement“, dass negative Effekte mindestens mit validierten Instrumenten zur Prä- und Post-Messung und für beide Behandlungsbedingungen erhoben werden sollten. Darüber hinaus sollen die Anzahlen derjenigen StudienteilnehmerInnen genannt werden, die keine positive Behandlungsreaktion zeigen oder gar eine reliable Verschlechterung der Symptome erleben [11]. In vielen Studien werden inzwischen der Reliable Change Index oder eine Symptomverschlechterung um 50 % zum Ausgangswert als Kriterien herangezogen. Der RCI erscheint sinnvoll, um sicherzustellen, dass die festgestellte Verschlechterung nicht auf Messfehlern basiert. Die Symptomverschlechterung um 50 % erscheint sinnvoll, um die unterschiedlich hohen Ausgangswerte einzubeziehen. Dennoch bleiben diese Vorgehensweisen willkürlich, da es bisher keinen Konsens darüber gibt, ab welchem Wert eine negative Veränderung tatsächlich eine kritische Veränderung darstellt. Weiterhin erscheint es notwendig, zwischen unerwünschten Nebenwirkungen („adverse events“) und schweren unerwünschten Nebenwirkungen („severe adverse events“) zu unterscheiden. Wie zuvor bereits beschrieben, könnten die Ergebnisse des INEP-Fragebogens in Studie 1 dazu verleiten, anzunehmen, die Intervention hätte erhebliche negative Auswirkungen

für die TeilnehmerInnen mit sich gebracht. Da hier zusätzlich auch noch der Vergleich mit der Kontrollgruppe nicht stattfinden konnte, weil der INEP-Fragebogen nur von den TeilnehmerInnen der Versuchsgruppe ausgefüllt wurde, sind die Ergebnisse nur begrenzt aussagekräftig. Rozental et al. definieren schwere Nebenwirkungen als negative Ereignisse, die während der Behandlung auftreten und zu einer Verschlechterung der Zielsymptome und / oder Nebenwirkungen führen und eine Form der unmittelbaren intensiven Behandlung erfordern, z.B. Alkohol- oder Drogenmissbrauch, vorsätzliche Selbstverletzung und suizidale Tendenzen oder gar Versuche, das eigene Leben zu beenden [11]. Die Nebeneffekte, die im INEP-Fragebogen angegeben werden, mit Ausnahme des Items zu Suizidabsichten, fallen nicht in diese Kategorie. Letztlich wäre noch eine Erhebung von Nebenwirkungen wünschenswert, die spezifisch bei internetbasierten Maßnahmen auftreten können und gegebenenfalls von hoher Tragweite sind, wie z.B. die eingeschränkte Erreichbarkeit von Kontaktpersonen (leitender Therapeut oder eCoach), Frust über technische Barrieren oder unzureichende Anleitung [179].

Die Teilnehmenden des RCTs (Studie 1) gaben darüber hinaus häufig an, negative soziale Konsequenzen zu fürchten, wenn andere Personen oder Institutionen von ihrer Teilnahme an einer psychologischen Intervention im Rahmen einer Depressionsstudie erfahren hätten. Die Angst vor Stigmatisierung scheint nach wie vor allgegenwärtig zu sein. Der Begriff „Stigmatisierung" wurde ursprünglich in der Soziologie von Erving Goffman als unerwünschte Andersheit gegenüber dem, was wir erwartet hätten, definiert. Hierbei spielen diskreditierende Attribute eine Rolle, die den gewöhnlichen Menschen abwerten und ausgrenzen [180]. Im Zusammenhang mit der mentalen Gesundheit geht es um ein anderes Erleben und Verhalten von Betroffenen und die damit einhergehende Angst, den sozialen Status und Ruf zu verlieren. In der Forschung ließ sich bereits zeigen, dass die eigene Einstellung zur psychischen Erkrankung einer Inanspruchnahme von psychotherapeutischen Angeboten erheblich im Wege steht [181] und auch die Adhärenz erheblich beeinflusst [182]. Allerdings zeigen Studien, dass Psychoedukation erheblich dazu beitragen kann, die stigmatisierende Haltung gegenüber psychischen Störungen zu reduzieren [183]. Wenn es gelingen würde, die Akzeptanz von Depressionen zu erhöhen, würde dies die Hemmschwelle erheblich reduzieren, Hilfe in Anspruch zu nehmen. So sollte frühzeitig Aufklärungsarbeit geleistet werden, insbesondere über die psychische Störung an sich, aber auch über verschiedene Behandlungsoptionen sowie ihre Vor- und Nachteile. Ebert et al. konnten in einem RCT zeigen, dass Informationsvideos die Akzeptanz internetbasierter Interventionen erhöhen können [184]. Dies könnte ein möglicher Weg sein, Nebenwirkungen im Zusammenhang mit negativen Erwartungen an die Intervention zu reduzieren. Da sich manche Nebenwirkungen nicht vermeiden lassen oder sie für den Behandlungserfolg gar erforderlich erscheinen, sollten Teilnehmende an derartigen Interventionen unbedingt zu Beginn darüber aufgeklärt werden. Findet diese Aufklärung nicht statt, kann es dazu führen, dass Teilnehmende die Interventionen abbrechen, sobald unangenehme Gefühle auftreten.

7. SCHLUSSFOLGERUNGEN

Internetbasierte Interventionen zur Behandlung von depressiver Symptomatik zeigten sich im Rahmen dieser Dissertation als effektiv in der Reduzierung depressiver Symptome. Für majore Depressionen traf dies auch im Vergleich zu einer Online-Psychoedukation zu. Die Wahl der Kontrollbedingung spielt für die Interpretation der Ergebnisse eine bedeutende Rolle und sollte auch in zukünftigen Studien mit Bedacht gewählt werden. Für subklinische Depressionen ließ sich eine Überlegenheit von internetbasierten Interventionen im Vergleich zu Kontrollgruppen kurz-, mittel- und sogar langfristig belegen. Darüber hinaus reduzierte sich das Risiko für die Entwicklung einer majoren Depression, wenn Betroffene an einer internetbasierten Intervention teilgenommen hatten.

Aktuell findet die Implementierung internetbasierter Maßnahmen in die Routineversorgung statt. Hierbei ist zu bedenken, dass die Effekte in der Praxis möglicherweise geringer ausfallen als in hoch strukturierten Studien. Gegebenenfalls müssen weitere Maßnahmen ergriffen werden, um eine vergleichbare Reichweite, Adhärenz und Effektivität von internetbasierten Interventionen in der Gesundheitsversorgung zu erzielen.

Es erfordert vielfältige weitere Forschung zu der Frage, wer von internetbasierten Maßnahmen zur Behandlung depressiver Symptomatik profitiert und wer nicht. Offenbar führt es zu besseren Ergebnissen, wenn sie in einem begleiteten Format stattfinden. Wie diese Begleitung genau auszusehen hat, um einen maximalen Nutzen zu erzielen, lässt sich auf Basis des aktuellen Forschungsstandes noch nicht genau definieren. Das Efficiency-Modell von Schueller et al. gibt jedoch gute Hinweise auf mögliche Fehlerpunkte, die es zu berücksichtigen gilt. Eine Individualisierung der Inhalte internetbasierter Interventionen erscheint unter diesem Aspekt in vielfacher Hinsicht notwendig und sinnvoll. Hierbei könnten unter anderem die initiale Symptomschwere, Alter, der Bildungsstand sowie die Erfahrung mit Psychotherapie berücksichtigt werden.

Es ließ sich zeigen, dass Teilnehmende an einer internetbasierten Intervention zur Behandlung majorer Depressionen sowie subklinischer Depressionen verglichen mit einer Kontrollgruppe ein niedrigeres Risiko für eine Symptomverschlechterung aufweisen. Die dritte Studie ergab hierfür keine signifikanten Gruppenunterschiede. Auch verändert sich die Einstellung zur Inanspruchnahme zukünftiger Therapieangebote offenbar nicht negativ bei denjenigen, die keine positive Behandlungsreaktion zeigten. Wie negative Effekte von internetbasierten Maßnahmen berichtet und dargestellt werden sollten, bedarf weiterer Einigung. Um sich der Fragestellung nach sinnvollen Zielkriterien anzunähern, gibt es dazu erste lohnenswerte Ansätze und Bestrebungen, beispielsweise das Consensus Statement von Rozental, 2014 [11] oder die Bemühungen des DELTA-Projekts [185].

Auf Basis der aktuellen Forschungslage erscheint es empfehlenswert, internetbasierte Maßnahmen als vollwertige Behandlungsalternative in die S3-Versorgungsleitlinie aufzunehmen, sowohl für leichte bis moderate als auch für majore Depressionen. Darüber hinaus sollte angestrebt werden, die Akzeptanz psychotherapeutischer Angebote im Allgemeinen und internetbasierter Interventionen im Speziellen zu erhöhen.

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9. ANHANG

Fachartikel 1: The more I got, the less I need? Efficacy of Internet-based guided self-help compared to online psychoeducation for Major Depressive Disorder

Fachartikel 2: Efficacy and moderators of psychological interventions in treating subclinical symptoms of depression and preventing major depressive disorder onsets: protocol for an individual patient data meta-analysis of randomised controlled trials

Fachartikel 3: Efficacy and moderators of internet-based psychological treatments in adults with subthreshold depression – an individual patient data meta-analysis of randomized controlled trials

Fachartikel 4: Does Internet-based guided-self-help for depression cause harm? An individual participant data meta-analysis on deterioration rates and its moderators in randomized controlled trials

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Research paper

The more I got, the less I need? Efficacy of Internet-based guided self-help compared to online psychoeducation for major depressive disorder

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ABSTRACT

Background: This study's aims were to compare the efficacy and negative effects of guided Internet-based cognitive behavior therapy (iCBT) and online psychoeducation (OPE) in people with major depression.
Methods: A total of 131 individuals were randomized. Assessments took place at baseline (T1), six weeks (T2), and three months (T3). The primary endpoint was change in observer-based depression severity from T1 to T2. Potential negative effects were analyzed in terms of suicidal ideations, symptom deterioration, attitudes toward seeking further help, and other adverse events.
Results: iCBT (n = 65) and OPE (n = 66) both reduced depressive symptoms from T1 to T2, with large changes observed for iCBT and medium for OPE (iCBT: Cohen's d = 1.09; OPE: d = 0.60). Differences between groups were significant at the primary endpoint (d = 0.36, p = 0.028). OPE continued to have a positive effect from post-treatment to follow-up, while the effect of iCBT remained stable, with differences between groups not being significant anymore at follow-up. Participants who had undergone prior psychotherapy benefited from both treatments; but for those without prior psychotherapy, iCBT was superior also at follow-up. In the iCBT group 26.2% of the participants reported at least one side-effect.
Limitations: The history of psychotherapy was imbalanced between the groups. Some negative effects were assessed in the iCBT group only.
Conclusions: Both iCBT and OPE were effective in reducing depressive symptoms, but with iCBT having a more rapid effect. iCBT was specifically superior in those with no prior history of psychotherapy. Negative effects occurred frequently and should be considered when implementing iCBT.
Trial registration: German clinical trials register: DRKS00005025

Background

Although numerous studies provide evidence supporting the efficacy of available psychological and pharmacological treatments for major depressive disorder (MDD) (Cuijpers et al., 2014a, 2008), most affected individuals remain untreated (Bebbington et al., 2003; Kessler et al., 2001; Mack et al., 2014). Reasons for these seemingly low treatment rates do not appear to solely relate to supply shortfalls — like prolonged waiting times, or long distances to therapy in rural areas. Anticipating negative (social) consequences, a low perceived need for treatment, and a preference for self-help are major barriers against seeking help (Andrade et al., 2014).

Internet-based self-help interventions could aid in solving some of these difficulties. Meta-analysis evidence indicates the efficacy of guided Internet-based interventions for major depressive disorder, in terms of large pre-to-post reductions in depressive symptoms, ranging from Hedges' g = 0.64 to g = 2.24, and beneficial effects when compared to controls (g = 0.90) (Königbauer et al., 2017). However, one criticism is that many comparisons in this field rely on control conditions, like a waiting list with no active intervention component. These comparisons convey only little regarding the efficacy of this strategy of treatment delivery at the current level of research (Kiluk et al., 2011).

Nowadays, it is increasingly common to use brief unguided self-help interventions, like online psychoeducation (OPE), as an active control condition for testing the effectiveness of Internet-based guided self-help interventions (Karyotaki et al., 2018). Furthermore, online psychoeducational information represents a realistic condition of care as usual in health information seeking behavior as the Internet may be the first source for most people who search for health information (Jacobs et al., 2017). There is evidence that psychoeducation can also be effective at

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reducing depressive symptoms, in terms of within-group effects, with effect sizes ranging from Cohen's d = 0.29 to d = 0.65 (Beiwinkel et al., 2017; Buntrock et al., 2015; Christensen et al., 2004; Imamura et al., 2016; Nobis et al., 2015). However, little is known about the comparative efficacy of online psychoeducation versus guided Internet-based cognitive behavior therapy (iCBT) for adult depression. Such comparisons are scarce and reveal mixed results, with some studies yielding medium to large between-group differences, favoring iCBT over OPE (d = 0.41 to d = 0.89) (Beiwinkel et al., 2017; Buntrock et al., 2015; Nobis et al., 2015), while other studies have generated non-significant differences (Christensen et al., 2004).

Given the high prevalence (Kessler, 2005; Wittchen et al., 2011) and the chronic nature of depressive illness (Eaton et al., 2008), MDD is responsible for high medical service use (Greenberg and Birnbaum, 2005). In the literature, there are indications that people with depression repeatedly seek psychological treatment (Bender et al., 2001; Comninos and Grenyer, 2007). Research on the impact of past psychotherapy on psychological intervention success is scarce and mixed in its findings. One study showed a higher likelihood for significant change in depressive symptoms if people had no previous history of mental health service utilization (Boswell et al., 2012), while other studies found no significant correlations between previous psychotherapy and treatment efficacy (Button et al., 2012; Grenyer et al., 2008; Junge et al., 2015). Thus, it also seems worthwhile to acquire further insights into how previous psychotherapy experiences influence Internet-based intervention success.

However, while Internet-based guided self-help interventions are assumed to have great potential for decreasing depressive symptoms, there also might be negative effects associated with participating in online psychological treatments; for example, symptom deterioration, negative intrapersonal changes, suicidal ideations, and adverse effects on intimate relationships (Rozental et al., 2014). A recent meta-analysis on Internet-based guided self-help treatments identified a significantly-lower risk of 'reliable deterioration' amongst those in the intervention group than in waiting list controls (Ebert et al., 2016a). However, there are unfortunately only very few investigators reporting non-responder rates, or the frequency of symptom deterioration, negative effects on help-seeking attitudes, and other adverse events (Boettcher et al., 2014; Ebert et al., 2018). Further analysis of the different domains of negative effects seems mandatory, given the increasing use of internet-based interventions (Boettcher et al., 2014; Emmelkamp et al., 2014; Rozental et al., 2014).

Objectives

The primary aim of this study was to compare the efficacy of a guided self-help iCBT (a shortened version of GET.ON Mood Enhancer) against an online psychoeducational module on depression. We further aimed to compare a range of secondary outcome variables (i.e. mental and physical health, clinical response, and reliable change and remission rates), as well as potential negative effects of treatment.

Methods

Study design and sample size

A guided self-help iCBT group was compared to an online psychoeducation group, with full access to usual treatment for both treatment arms. Assessments took place at baseline (T1), as well as six weeks (T2) and 12 weeks (T3) after randomization. Recruitment started in May 2013 and ended in March 2014. Power analysis (calculated using PASS 12) indicated that 128 subjects were required to detect a between-group effect size of d = 0.50 (power = 80%; $\alpha = 0.05$). Further details on study design have been published elsewhere (Ebert et al., 2014a).

Participants and procedures

Recruitment

A major scope of our research group was to develop interventions for various levels of depressive symptoms. Consequently, we evaluated two versions of an Internet-based program, called GET.ON Mood Enhancer, in two independent randomized controlled trials at the same time. For the first of these trials, the sample population had subthreshold depression (trial registration: DRKS00004709) (Buntrock et al., 2014). The currently-presented trial used a shortened version of the intervention to be evaluated in a sample with MDD. Participants were primarily recruited from the general population via a large German health insurance company, as well as through on-air media, newspaper articles, and related websites (GesundheitsTraining.online, 2014). Those interested in participating were invited to send an e-mail to the research team or apply online on the research website, where they were asked to provide their e-mail address.

Inclusion and exclusion criteria

All subjects had to a) be ≥ 18 years of age; b) be diagnosed with MDD, according to DSM-IV-criteria assessed via SCID (First et al., 2002); c) have Internet access; d) possess sufficient German skills both for reading and writing; and e) agree to the terms of the trial by providing informed written consent. Individuals were excluded if they a) had a history of manic/hypomanic episodes; b) had a history of psychotic disorders; c) were currently receiving psychotherapy for any kind of mental health problem; d) exhibited a notable suicidal risk, as indicated by a score greater than 1 on item 9 of the Beck Depression Inventory (BDI (Beck et al., 1996); 'I feel I would be better off dead'); or e) had changed either their antidepressant medication or its dose over the four weeks prior to the baseline assessment.

Assessment of eligibility and randomization

Applicants who met all inclusion and none of the exclusion criteria were permitted to enter the study, at which time they were randomly allocated — using an automated computer-based random integer generator (randlist) — to either of the two study conditions by an independent researcher who was not otherwise involved in the study.

Intervention conditions

Guided Internet-based cognitive behavioral therapy. The guided self-help iCBT intervention — GET.ON Mood Enhancer — consists of six interactive sessions. Each session lasts about 30 min, though the duration might vary between users. Since a previous meta-regression analysis indicated that more frequent therapy sessions may be associated with better outcomes than less frequent sessions (Cuijpers et al., 2013), participants were advised to finish at least one, but preferably two modules per week. The program was also available beyond the post assessment at 6 weeks.

The modules rely on evidence-based face-to-face manuals that have been shown to be effective at reducing depressive symptomatology, including psychoeducation, and exercises for behavioral activation, problem solving, and relapse prevention; with three additional modules (sleep problems, relaxation techniques, worrying) that can be chosen, depending on individual users' needs or preferences. A strong emphasis was placed on homework assignments designed to integrate acquired coping skills into daily life. Relative to the standard version of the intervention, which was originally developed to target subclinical depressive symptoms, and proven to be both effective (Buntrock et al., 2016a; Ebert et al., 2018; Ebert et al., 2016b; Nobis et al., 2015) and cost-effective (Buntrock et al., 2017) across a range of target conditions, the current version was shortened and simplified to account for potentially-reduced ability to concentrate among individuals with severe depression. Changes to the standard version included reducing the lengths of explanatory text, as well as reducing the choice options for participants (e.g., elective modules like increasing social support,

progressive muscle relaxation). Participants were supported by eCoaches (psychotherapists-in-training supervised by an experienced clinician). Guidance took place in the form of individualized written feedback after each module. The total time an eCoach spent per user averaged two hours. All feedback was stored for supervision and adherence checks.

Online psychoeducation on depression. The online psychoeducation intervention used the same platform as GET.ON Mood Enhancer. It was based on the patient version of the National Disease Management Guideline Unipolar Depression (VersorgungsLeitlinien.de, 2009). Participants were informed about the nature of depression, its symptoms, and strategies to overcome depressive episodes, including existing evidence-based treatments and sources of help. Neither specific homework assignments nor any eCoach support was provided. This online psychoeducation module has been shown to reduce the severity of depressive symptoms in patients with concomitant depression and diabetes (Nobis et al., 2015), and in a sample with subthreshold depressive symptoms (Buntrock et al., 2015).

Treatment as usual. At the end of both treatments participants received information of how to access further help and were encouraged to use routine mental health services, like psychotherapy or antidepressant medication, throughout the study period. However, we monitored treatment utilization and changes in antidepressant medication doses over the trial period to control for potential confounding.

Primary and secondary outcomes

Change in observer-based depression severity from baseline to posttreatment was considered the primary outcome. Secondary outcome measures were used to explore treatment effects on self-reported depressive symptomatology, anxiety symptoms, overall well-being, and general physical and mental health, as well as the rates of response, remission, and reliable improvement in the two study groups. We also evaluated for potential negative effects, including reliable symptom deterioration, effects on attitudes toward seeking psychological help, and other adverse events deemed attributable to the GET.ON Mood Enhancer program.

Measures

Primary outcome. Observer-based depression severity was measured using the widely used Hamilton Rating Scale for Depression, HRSD-24 (Hamilton, 1960; Miller et al., 1984). The HRSD contains depressed mood, vegetative and cognitive symptoms of depression, and anxiety symptoms. In this study, the HRSD-24 exhibited very good inter-rater reliability, with an intraclass correlation coefficient (ICC) of 0.97 (95%-CI: 0.91–0.99) at T2, based on recorded audio data from randomly-selected participants (10% of cases). In two subjects, assessor blinding to treatment condition was violated. In these cases the interviewer was changed for the following assessment.

Secondary outcomes

Mental and physical health. We also used a second observer-based rating of depression: the Quick Inventory of Depressive Symptomatology - Clinician-Rating QIDS-CR16 (Rush et al., 2003; Trivedi et al., 2004). Contrary to the HRSD, it only addresses the nine depression criteria from the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2000) over the preceding seven days. The Patient Health Questionnaire, PHQ-9 (Kroenke and Spitzer, 2002, 2001), was used to assess depressive symptomatology by self-report. Contrary to the primary outcome measure, HRSD-24, the PHQ-9 does not assess the intensity, but rather the frequency of symptoms, in nine items. Anxiety was measured with the anxiety subscale of the Hospital Anxiety and Depression Scale HADS-A (Zigmond and Snaith, 1983). The SF-12v1 Health Survey (Gandek et al., 1998) was used to assess health-related quality of life. We used two subscales of the Social Problem-Solving Inventory-Revised, SPSI-R (D'Zurilla et al., 2002), to measure problem-solving ability: the positive problem orientation (PPO) subscale measures a constructive dimension; while the negative problem orientation (NPO) subscale can be seen as a dimension of dysfunction. The Behavioral Activation for Depression Scale-Short Form, BADS-SF (Fuhr et al., 2016), was used to measure participants' active motivation for goals or values, as well as pleasant activities and avoidance behaviors. Psychological well-being was measured using the World Health Organization's (WHO) 5 Wellbeing Index (Primack, 2003).

Clinical significance. To assess improvements in the primary outcome at an individual level, for both study groups we examined according to the study protocol a) the number of participants with a clinical response, defined as 50% reduction from baseline symptom severity (Rush et al., 2006); and b) the number of participants exhibiting 'reliable improvement', employing the widely-used reliable change index (RCI) proposed by Jacobson and Truax, 1991. Participants were defined as reliably improved if their HRSD-24-score declined, from baseline to post-assessment, with a reliable change index greater than 1.96 (one standard deviation, which equaled 4.42 points on the HRSD-24, based on $SD_{post} = 9.2$ and $ICC_{post} = 0.97$). In addition, we examined c) the number of participants who exhibited complete remission of their depression, defined a-priori as a post-assessment HRSD-24 score ≤ 10 (Kyle et al., 2016).

Adverse effects from the Internet-based intervention. According to Rozental et al., 2014, adverse effects should be analyzed in multitude domains. Increased suicidal risk of subjects in either group over the study course is one potential negative effect. A clinically-significant increase in the suicidal ideation item score on the HRSD-24 from baseline to post-treatment or follow-up was considered any increase ≥ 2 (0 = "Absent", 1 = "Feels life is not worth living", 2 = "Wishes he were dead or any thoughts of possible death to self", 3 = "Suicidal ideas, gestures, or plans", 4 = "Attempted suicide"). A score of 3 or 4 was considered a severe risk.

We also measured depressive symptom deterioration over the course of treatment. Participants were coded as having 'deteriorated' if they experienced a reliable negative change (-1.96) in the HRSD-24, as per RCI.

The Inventory of Negative Effects in Psychotherapy, INEP (Ladwig et al., 2014), was used to measure other adverse events. The version used in this study consists of 15 items that inquired about any negative effects that individuals experienced during or after completion of the Internet-based training program that were attributed to the program itself, including a) negative intrapersonal changes; b) negative changes in an intimate relationship; c) adverse effects on family/friends; d) perceived dependence on the psychotherapist/psychotherapeutic intervention; and e) stigmatization. The items are rated on a 7-point Likert scale that ranges from -3 (very negative experience) to $+3$ (very positive experience) or on a 4-point Likert scale that ranges from -3 (total agreement) to 0 (no agreement at all). Adverse events were counted by any negative response on one of the items.

To evaluate whether bad experiences with Internet-based interventions could have a negative effect on future utilization rates of other help, we used the Attitudes Toward Seeking Professional Psychological Help Scale-SF, ATSPPH-SF (Fischer and Farina, 1995), to measure potential negative influences on attitudes toward seeking mental health-care service utilization in participants who did not respond to their allocated intervention (Ebert et al., 2018).

Course evaluation. User satisfaction was measured with the CSQ-I (Boss et al., 2016). This questionnaire consists of eight items measuring global client satisfaction.

Data analysis

All analyses followed an intention-to-treat (ITT) protocol, including

all participants who were randomly assigned to either of the two study groups, regardless of nonadherence to the intervention or non-attendance at follow-up assessments. For all ITT analyses, missing data were handled via multiple imputations (Schafer and Graham, 2002). Hundred single imputations of the missing values were calculated based on the valid data for all outcome measures at all assessment points (T1, T2, and T3) as well as age and gender and were aggregated into a single overall estimate of each outcome variable.

As a first step of our primary analysis, we examined for group differences in the primary outcome variable over time by employing mixed effects models, with fixed effects for *symptomatology, group*, and *assessment point,* and a random intercept to account for clustering within each participant. The model also included a twofold interaction term — *group x assessment point* — allowing us to analyze for differences in the intervention effect between baseline (T1) and the two follow-up assessments (T2 and T3). Although the study was initially not powered to identify moderators, we conducted a second analysis step because of baseline imbalances in the number of participants with a history of psychotherapy between the study groups. This incorporated a fixed effect for *history of psychotherapy* (yes/no), a twofold interaction term — *assessment point x history of psychotherapy* — and a three-factor interaction term — *assessment point x group x history of psychotherapy*. For this, we deviated from the initial study protocol to adjust for covariate imbalances at baseline, as recommended by Pocock et al., 2002. The fixed effect of most interest was the *assessment point* × *group* interaction, which indicated that the difference between the intervention and control groups was a change in psychopathological symptoms over time. We calculated Cohen's d with 95% confidence intervals (Cohen, 1988) for pre-to-post differences on the primary outcome for each study group. Additionally, we calculated Cohen's d for all intergroup differences by subtracting the difference between baseline and follow-up in the online psychoeducation group from the difference between baseline and follow-up in the iCBT group, and dividing this by the pooled standard deviation of the change scores.

Clinical response, reliable improvement, remission, increased suicidal risk and deterioration rates were analyzed using contingency tables and Pearson $\chi 2$ analysis. For significant findings, we also calculated the number needed-to-treat (NNT, with 95% confidence intervals) with GET.ON Mood Enhancer to achieve one additional response, one reliable change, and one remission, relative to online psychoeducation.

In a pre-planned subgroup analysis, we explored negative effects of the GET.ON Mood Enhancer program on attitudes toward seeking psychological help in participants who did not reach the response criteria by T2. To investigate the hypothesis that GET.ON Mood Enhancer does not lead to more negative attitudes toward psychological interventions among those who failed to experience a clinical response, relative to online psychoeducation, a confidence interval approach was used for the effect size of the difference between the two treatment groups. The equivalence margin that corresponds to the smallest value that would represent a relevant negative effect was set, *a priori*, at d = −0.20, which has been set 20% lower compared to what has been defined as a minimal important difference in the treatment of depression (Cuijpers et al., 2014b). The lower bound of the 95% CI for the effect size was compared with the predefined equivalence margin of d = −0.20, and had to be above the margin to exhibit equivalence. One-sided hypotheses were tested using one-sided tests; while two-sided hypotheses (e.g., tests on negative effects) were conducted using two-sided test. The *a priori* criterion for statistical significance was set at $p < 0.05$.

Results

Participant flow

In total, 131 individuals gave their informed consent and were randomized into the two study groups (Fig. 1). Participants were predominantly female (n = 99; 75.6%), with an average age of 41.6 years (SD = 10.8; Table 1). Nearly half of the participants (n = 60; 45.8%) suffered from a chronic course of depression. There were no meaningful differences in baseline characteristics between the groups, except for the number of participants with a history of psychotherapy, who were overrepresented in the Internet-based self-help cognitive behavioral therapy (iCBT, n = 45; 69.2%) group relative to the online psychoeducation (OPE, n = 32; 48.5%) group. Therefore, we included 'history of psychotherapy' as a baseline predictor in a separate mixed-effects model, to analyze its impact on the primary outcome.

Intervention usage and service utilization

Of the 65 participants in the iCBT group, 63 (96.9%) completed at least one training module, 61 (93.8%) completed two modules, 60 (92.3%) completed three, 54 (83.1%) completed four, 52 (80%) completed five, and 49 (75.4%) completed all six modules of the intervention. In the iCBT group 37 participants (56.9%) finished the training prior to the post-assessment and 24 (36.9%) continued with the training afterwards. Participants needed an average of 39 days to complete the program (SD = 20.8; range 3 – 87 days). Of the 66 participants in the OPE group, 53 (80.3%) read the psychoeducation material, as determined by their log-in history.

In the iCBT group, eight (12.3%) experienced some change (drug or dose) in their anti-depressant medication, while nine (13.8%) began psychotherapy over the course of the study, with two withdrawing from the study for the latter reason. Baseline data from these two participants was included in the analyses. Missing values at the post- and follow-up-assessment were handled like other missing data by multiple imputations in accordance to the intention to treat principle. Among those participants receiving psychoeducation, six (9.1%) experienced some change in their medication, while seven (10.6%) began psychotherapy.

Primary outcome analysis

Both study groups exhibited statistically-significant reductions in observer-based depression severity from baseline (T1) to post-treatment scores (T2) on the HRSD (Table 2). Mixed-effects model (MEM) analysis of the base model, unadjusted for any baseline imbalances, showed that in those who received iCBT, there was a mean reduction of 8.31 points on the HRSD ($p < 0.001$; d = 1.09, 95% CI 0.72–1.46). In the OPE group, the mean reduction on the HRSD was 5.42 points ($p < 0.001$; d = 0.59, 0.24–0.94). Both groups also exhibited significant decreases from T1 to 3-month follow-up (T3), of 8.62 points in the iCBT group ($p < 0.001$; d = 1.02, 0.65–1.38) and 7.70 points in their OPE counterparts ($p < 0.001$; d = 0.87, 0.51–1.23). The analysis of group differences revealed a significantly-greater reduction in depression severity from T1 to T2 with iCBT than with OPE (*T1-T2 x group:* $p = 0.028$; d = 0.36, 0.01–0.70). However, there was no difference in change from T1 to T3 between the groups (T1-T3 x group: $p = 0.197$).

Following our analysis plan, we conducted further MEM analyses including *baseline psychotherapy history* (yes/no) as a predictor and potential moderator of change in observer-based depression severity over time (Tables 3, 4). The adjusted MEM revealed a) a significant decrease in depression severity from baseline to post-treatment (*T1-T2*, Table 3) and from baseline to final follow-up (*T1-T3*) with both iCBT and OPE; and b) a significantly-greater reduction in depression severity only among participants in the OPE who had undergone psychotherapy prior to their entry into the current study (*T1-T2 x psychotherapy history/ T1-T3 x psychotherapy history*) versus those with no psychotherapy history. The twofold interaction (*T1-T2 x group*, Table 4) indicated c) a significantly-greater decrease (− 7.1 HRSD points) in depression severity from baseline to T2 in the iCBT than OPE group, among participants with no psychotherapy history. Finally, d) a significantly-positive threefold interaction coefficient (*T1-T2 x psychotherapy history x group*) indicated that, comparing the reduction in depression severity

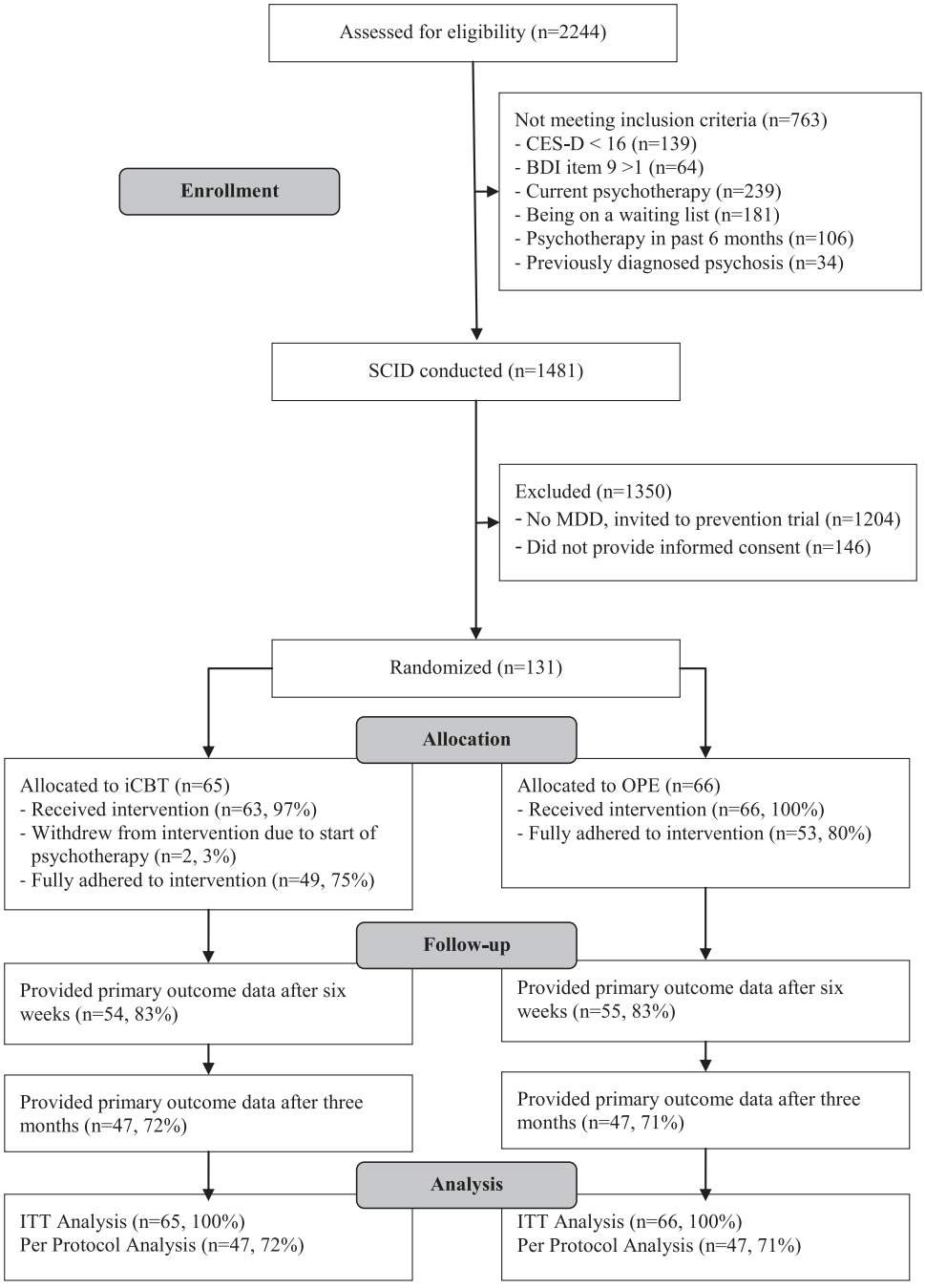

Fig. 1. Study Flow.

from T1 to T2 between participants with versus without a psychotherapy history, the mean T1-T2 difference was smaller in those receiving iCBT than those receiving OPE. The contrary impact of this interaction on the change in depression severity over time in participants with compared to those without a psychotherapy history is depicted in Fig. 2. In summary, on MEM analysis adjusted for psychotherapy history, no difference was detected between the two treatment arms, in terms of T1-to-T2 depression severity among participants with a psychotherapy history (d = 0.09, 95% CI −0.37–0.54), but a significant difference in the two treatments was observed in those with no prior psychotherapy; and this effect was large (d = 0.82, 95% CI 0.25–1.40).

Secondary outcome analysis

Clinical significance

There were no significant differences between the two treatment groups in terms of the percentage of subjects experiencing a clinical response from T1 to T2 ($\chi^2 = 0.420$, $p = 0.279$) or from T1 to T3 ($\chi^2 = 0.062$, $p = 0.402$). There also were no significant inter-treatment differences in remission rates at either T2 ($\chi^2 = 0.654$, $p = 0.210$) or T3 ($\chi^2 = 0.374$, $p = 0.271$) (Fig. 3). In the iCBT versus OPE group, significantly more participants exhibited a reliable improvement in depression severity from T1 to T2 ($\chi^2 = 5.152$, $p = 0.012$), indicated by a number needed to treat to achieve one reliable improvement from T1 to T2 of 5.12 (95% CI 2.77–33.11). There was no significant inter-treatment difference from T1 to T3 ($\chi^2 = 0.719$, $p = 0.198$).

Table 1
Demographic characteristics: means/counts and standard deviations/percentages.

	All				iCBT				OPE			
	N	%	M	SD	N	%	M	SD	N	%	M	SD
Age			41.6	10.8			40.6	10.7			42.7	10.8
Females	99	75.6			45	69.2			54	81.8		
Married/partnership	61	46.6			27	41.5			34	51.5		
Higher education	94	71.8			44	67.7			50	75.8		
Currently employed	94	71.8			42	64.6			52	78.8		
Chronicity of MDD[a]	60	45.8			33	50.8			27	40.9		
Suicidal ideation at baseline[b]	8	6.1			4	6.2			4	6.1		
History of psychotherapy at baseline	77	58.8			45	69.2			32	48.5		
Baseline medication	26	19.8			14	21.5			12	18.2		
Started psychotherapy during treatment	16	12.2			9	13.8			7	10.6		
Changed medication during treatment	32	24.4			16	24.6			16	24.6		

Abbreviations: iCBT = Internet-based cognitive behavior therapy; OPE = online psychoeducation on depression;
[a] = referring to DSM-V criteria for chronic major depressive disorder;
[b] = as defined by a score of 2 on the Hamilton Rating Scale for Depression suicidal ideation item ("thoughts about being dead or of possible death to self").

Mental and physical health

To analyze intervention effects on continuous secondary outcomes, we used MEM adjusted for psychotherapy history, analogous to the primary outcome analysis model. Significant cross-level interaction effects indicated between-group differences in change from baseline to posttreatment (*T1-T2 × group*) that favored iCBT, with respect to improved severity of depression criteria symptoms (d = 0.36), self-rated depression (d = 0.25), behavioral activation (d = 1.16), and anxiety (d = 0.40; Table S1). No inter-group differences were identified for changes in overall well-being, problem-solving skills, or general physical health (Table S3). The cross-level interaction effect *T1–T3 × group* was significant only for behavioral activation (d = 0.70) and overall well-being (d = 0.44), indicating larger improvements in the iCBT than OPE group at T3 (Table S3). The threefold interaction effect *T1-T2 x psychotherapy history x group* only was significant for self-rated depression and anxiety, indicating a smaller difference between those with versus without prior psychotherapy in symptom reduction from baseline to post-treatment in participants in the iCBT than OPE group. Effect sizes and MEM coefficients for all secondary outcome variables are available for viewing in downloadable supplemental tables.

Adverse effects from the Internet-based intervention

Suicidal ideations

In the iCBT and OPE groups, four (7.4%) and one subject (1.9%), respectively, reported "thoughts about being dead or of possible death to self" (score = 2 on the HRSD-24 suicide item) at any time over the week prior to the T2 interview. At T3, corresponding numbers were four (7.7%) and four (8.3%). Comparing to the baseline (Table 1), the prevalence of suicidal ideation remained stable in both groups. All suicidal ideations were documented by the interviewer and corresponding subjects supervised by an experienced clinician. No participant in either treatment arm reported suicidal ideas, gestures, plans, or attempts (HRSD-24 suicide item score = 3 or 4).

Reliable deterioration in depressive symptoms

Assessing the number of participants with increased baseline symptomatology (≥ 4.42 points on the HRSD-24), six (9.2%) and five (7.6%) of the subjects in the iCBT and OPE groups experienced a reliable deterioration from T1 to T2, respectively; these rates were not statistically different ($\chi^2 = 0.117$, $p = 0.732$). From T1 to T3, corresponding numbers with reliable symptom deterioration were three (4.6%) and six (9.1%), a difference that, again, was not statistically significant ($\chi^2 = 0.311$, $p = 0.492$). There was no association between the deterioration rates and adherence to the intervention from T1 to T2

Table 2
Means and standard deviations of outcome variables at baseline, post-treatment, and at three-month follow-up based on multiple imputations (intention-to-treat sample).

	T1				T2				T3			
	iCBT		OPE		iCBT		OPE		iCBT		OPE	
Outcome	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
HRSD	22.06	7.71	21.83	8.62	13.75	7.52	16.47	9.45	13.44	9.19	14.39	8.49
QIDS	12.02	4.49	11.82	4.43	7.99	4.53	9.46	5.14	7.74	4.84	7.98	4.49
PHQ-D	15.72	4.41	16.06	4.31	10.62	4.99	12.11	5.44	10.35	5.15	11.09	5.42
BADS	19.35	6.58	22.00	6.60	28.86	8.97	23.96	8.35	27.46	9.03	25.75	8.60
HADS-A	11.82	3.91	11.72	3.20	8.90	4.26	10.08	4.39	8.99	4.00	9.51	3.55
WHO5	4.49	2.87	4.35	2.75	7.82	4.63	6.47	4.52	8.67	5.08	7.59	4.95
SPSI-PPO	7.54	3.81	7.75	4.57	9.87	3.44	8.76	4.19	9.67	3.88	8.70	4.09
SPSI-NPO	8.39	4.77	8.13	5.08	6.98	4.27	8.21	4.98	6.90	4.35	7.73	4.50
SF12-PH	44.59	11.10	46.16	8.68	43.12	10.92	45.81	9.68	44.20	10.34	46.43	10.02
SF12-MH	26.84	7.10	26.52	6.85	34.93	10.10	31.74	10.13	36.67	10.62	35.04	9.53
ATSPPH	21.72	4.32	21.24	4.41	22.00	3.91	21.57	4.34	/	/	/	/

Abbreviations: T1 = baseline; T2 = post-treatment after six weeks; T3 = follow-up after three months; iCBT = Internet-based cognitive behavior therapy; OPE = online psychoeducation on depression; / = No assessment; HRSD = Hamilton Rating Scale for Depression; QIDS = Quick Inventory of Depressive Symptomatology - Clinician-Rating; PHQ = Patient Health Questionnaire-Depression; BADS = Behavioral Activation Depression Scale; HADS-A = Hospital Anxiety and Depression Scale – Anxiety Subscale; WHO5 = World Health Organization's 5 Wellbeing Index; SPSI-PPO = Social Problem-Solving Inventory – Positive Problem Orientation; SPSI-NPO = Social Problem-Solving Inventory – Negative Problem Orientation; SF12-PH= SF-12 Health Survey – Physical Health Subdomain; SF12-MH = SF-12 Health Survey – Mental Health Subdomain; ATSPH = Attitudes Toward Seeking Professional Psychological Help.

Table 3
Estimated differences in change from baseline to six weeks and three month follow-up of the primary outcome in each group based on mixed-effect-model including psychotherapy history, time, and its interaction as predictors.

	Intercept Baseline		Psychotherapy history		T1-T2		T1-T2 x Psychotherapy history		T1-T3		T1-T3 x Psychotherapy history	
	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE
iCBT	18.47	1.47	5.19[a]	1.51	−9.85[a]	1.78	2.21	2.09	−8.73[a]	1.78	−0.13	2.09
OPE	19.46	1.26	5.19[a]	1.51	−2.73[c]	1.40	−5.72[b]	1.95	−5.52[a]	1.40	−4.25[c]	1.95

Abbreviations:
[a] $=p < 0.001$;
[b] $=p < 0.01$;
[c] $=p < 0.05$; [d] $= p < 0.10$; T1 = baseline; T3 = follow-up after three months; iCBT = Internet-based cognitive behavior therapy; OPE = online psychoeducation on depression.

($\chi^2 = 1.520$, $p = 0.252$) or from T1 to T3 ($\chi^2 = 2.135$, $p = 0.222$). There was also no association between deterioration and study attrition from T1 to T2 ($\chi^2 = 0.011$, $p = 1.000$) or from T1 to T3 ($\chi^2 = 0.024$, $p = 1.000$).

Attitudes toward seeking help

Potential negative effects on help-seeking attitudes (ATSPPH) were examined in participants who did not reach our *a priori* criterion for a clinical response (iCBT: n = 46, 70.8%; OPE: n = 50, 75.8%). Attitudes toward seeking psychological help increased in both study groups (iCBT: 0.28 points; OPE: 0.33 points), with no significant difference between the two treatments (T1-T2 x group, $p = 0.321$; d = 0.04; 95%-CI −0.37 to 0.46). As the effect sizes were positive and did not cross the lower bound of the confidence interval for the predefined equivalence margin of d = −0.20, it can be concluded that there were no negative effects on attitudes toward seeking psychological help in those who failed to respond to the intervention.

Other negative side-effects

At T2, 17 of the 65 subjects (26.2%) in the iCBT group reported negative side-effects that they attributed to participating in the intervention. Most frequently, they reported effects in the area of negative intrapersonal changes, with most ratings on the item “During the training or since completing the training there were phases I was feeling mentally unwell.” (n = 6, 9.2%). Some reported perceived stigmatization, partnership problems, problems with family or friends, or perceived dependence on the eCoach (Table S4).

Program evaluation

Among those in the iCBT group, 45 of the 54 who answered questions on their satisfaction with the program (83.4%) said that they were satisfied, overall, with the intervention. The majority perceived the training as being of high quality (n = 50, 92.6%), and said they: received the kind of training they had wanted to receive (n = 43, 79.6%); perceived that their needs had been met (n = 41, 75.9%); were satisfied with the amount of assistance they received (n = 39, 72.2%); would use the program again, should the need arise (n = 48, 88.9%); found that the training helped them to deal effectively with their problems (n = 41, 79.9%). Forty-seven of the 54 (87.0%) said they would recommend the intervention to a friend.

Discussion

Primary outcome

In the current randomized controlled trial, a shortened version of original GET.ON Mood Enhancer program was associated with significant improvements in depressive symptoms in a sample of moderate to severely depressed individuals with Major Depressive Disorder and a high chronicity of depressive symptoms. Large effects were found in changes of observer-based depression severity from baseline to immediately post-treatment (d = 1.10) and three-month follow-up (d = 1.01). These findings are consistent with those of a recent meta-analysis on internet- and mobile-based depression interventions for those with diagnosed depression (Königbauer et al., 2017). Results are also in line with the findings from earlier studies that our group has conducted using other (non-shortened) versions of GET.ON Mood Enhancer, which yielded within-group-effects of d = 1.06 in those with subthreshold depressive symptoms (Buntrock et al., 2015). However, changes were somewhat smaller compared to findings in a group of patients with diabetes mellitus and co-morbid depression with effects of d = 1.40 (Nobis et al., 2015).

Surprisingly, participants in our trial who received online psychoeducation also experienced substantial reductions in observer-based depression severity from baseline to immediate post-treatment, with a medium within-group effect of d = 0.60 and a large effect for changes from baseline to follow-up (d = 0.87). This result is somewhat higher than findings from earlier studies on guided iCBT interventions, in which only small within-group effects were observed for online psychoeducation (Beiwinkel et al., 2017), even in studies of our own group that used exactly the same online psychoeducation intervention (Buntrock et al., 2015; Ebert et al., 2017; Nobis et al., 2015).

In the first step of mixed-effect-model (MEM) analysis, unadjusted for any baseline imbalances, we found a significant superiority of GET.ON Mood Enhancer over OPE at the primary endpoint post-

Table 4
Estimated group differences of the primary outcome based on mixed-effect-model including two- and threefold interaction terms with group, time, and history of psychotherapy as predictors.

Group Baseline		T1-T2 x Group				T1-T2 x Psychotherapy history x Group				T1-T3 x Group				T1-T3 x Psychotherapy history x Group			
B	SE	B	SE	CI_{low}	CI_{upp}	B	SE	CI_{low}	CI_{upp}	B	SE	CI_{low}	CI_{upp}	B	SE	CI_{low}	CI_{upp}
−0.99	1.49	−7.12[b]	2.18	2.84	11.40	7.94[b]	2.64	2.75	13.12	−3.20[d]	2.18	−7.48	1.08	4.12[d]	2.64	−1.07	9.31

Abbreviations:
[a] $=p < 0.001$;
[b] $=p < 0.01$;
[c] $=p < 0.05$;
[d] $= p < 0.10$; T1 = baseline; T3 = follow-up after three months; negative coefficients indicate a decreased depression severity for Internet-based cognitive behavior therapy compared to online psychoeducation on depression.

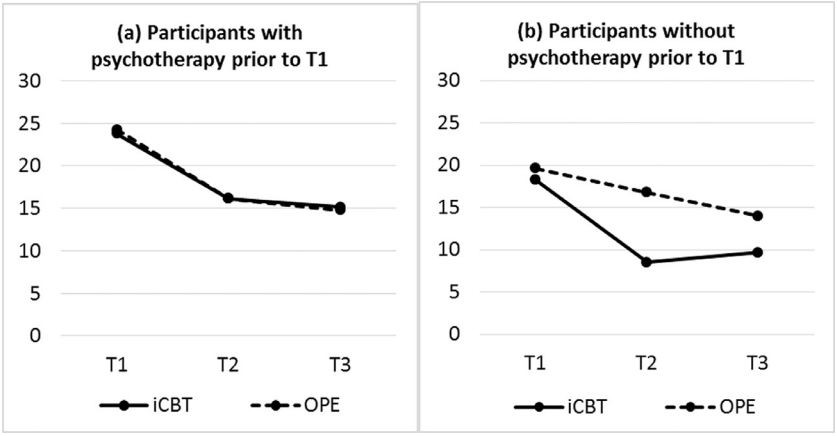

Fig. 2. Course of depressive symptomatology on the HRSD in the subgroups of participants (a) with and (b) without psychotherapy experiences prior to the baseline assessment. T1 = baseline; T2 = post-treatment after six weeks; T3 = follow-up after three months; iCBT = Internet-based cognitive behavior therapy; OPE = online psychoeducation on depression.

treatment, with a small to medium between-group effect of d = 0.36, but no differences for change from baseline to follow-up. Results from previous comparable studies are inconsistent, however, some identifying no between-group effects at all (Christensen et al., 2004), while others using the original non-shortened version of GET.ON Mood Enhancer, found medium (Buntrock et al., 2015) or large between-group effects in favor of iCBT both in short-term (Nobis et al., 2015) and in long-term (Buntrock et al., 2016b; Ebert et al., 2017). Interestingly, the mean values indicated a stable effect for iCBT between T2 and T3, while psychoeducation initially showed a lower improvement, but continued to have a positive impact on depression severity from post-treatment to follow-up. These results indicate that both kinds of interventions can reduce depression severity, but iCBT might work more rapidly than psychoeducation. An explanation for the non-superiority of iCBT vs. psychoeducation at follow-up might lie in the fact that we tested a shortened version of the GET.ON Mood Enhancer intervention, because we wanted to account for potential concentration difficulties in subjects with severe depression. However, this might have led to a lower perceived credibility or inadequate intervention intensity for some participants and not enough additional value of guided self-help vs. psychoeducation. Such an assumption is supported by the fact that satisfaction ratings in the present trial were lower than in various previous studies that utilized the original, longer version of GET.ON Mood Enhancer (Buntrock et al., 2015; Ebert et al., 2018; Nobis et al., 2015). An alternative explanation for the lower satisfaction rates and non-superiority of guided-self-help vs. psychoeducation compared to prior evaluations might be associated with differences in the various samples' baseline characteristics, such as the large proportion (51%) of individuals that reported chronicity of their depressive symptoms at baseline.

When we included baseline psychotherapy history as a potential predictor and moderator of change in an adjusted MEM, we only found the iCBT program to be superior to OPE, in terms of reducing observer-based depression severity from T1 to T2, in people with no prior psychotherapy experience (between-group effect d = 0.87). No such significant effect was identified for those with a psychotherapy history (between-group effect d = 0.08). This is in line with Boswell et al., 2012, who found students to be more likely to experience a clinically-significant change in depressive symptoms if they had no history of psychotherapy. However, it is contrary to the results of Button et al., 2012 and Junge et al., 2015, who did not find previous psychotherapy to significantly predict or moderate iCBT efficacy.

Internet–based guided self-help might be especially beneficial compared to simple psychoeducation when the intervention is the first service that people with MDD use, because it contains specific therapeutic strategies that may provide a novel way for them to cope with their problems ("novelty hypothesis"). This possible explanation links to the phase model of psychotherapy outcomes (Howard et al., 1993), a model that describes different treatment phases to go along with different experiences that individuals have with regard to changes in symptoms and well-being. On the other hand, for recurrent help seekers who have already accumulated knowledge from previous treatments,

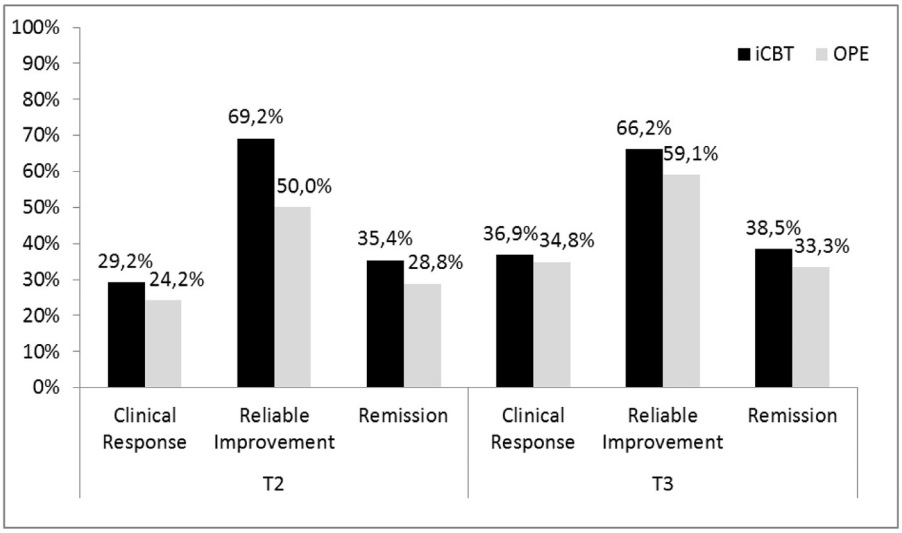

Fig. 3. Rates of clinical response, reliable improvement, and remission. T1 = baseline; T2 = post-treatment after six weeks; T3 = follow-up after three months; iCBT = Internet-based cognitive behavior therapy; OPE = online psychoeducation on depression.

online psychoeducation might be a kind of refresher course, unearthing previously-learned knowledge and coping behaviors to address their depressive episode ("refreshing hypothesis"). For these people, guided self-help might provide no meaningful incremental benefit over and above a psychoeducational refresher course, which might be sufficient for at least some patients. Such an assumption is supported by our finding that average pre-post changes of participants in the psychoeducation group with no previous experience in psychotherapy were significantly larger (d = 1.18) than in those with prior psychotherapy (d = 0.31). Future studies are needed to test this assumption.

Secondary outcomes

We analyzed intervention effects on several secondary outcomes. While significantly more participants in the iCBT versus OPE group experienced a reliable improvement in their depression scores immediately post-treatment, no between-treatment differences were found in either the rate of clinical response or the rate of remission, either immediately post intervention or at 3-month follow-up. However, guided self-help iCBT was superior to online psychoeducation, with medium-to-large effects on behavioral activation, and small-to-medium effects on problem-solving skills and anxiety. These findings were expected, because the intervention emphasizes behavioral activation and problem solving, both of which have already been proven to be effective as stand-alone interventions (Ebert et al., 2014b; Ekers et al., 2014; Hoek et al., 2012).

Negative intervention effects

In this study, we systematically analyzed potential negative effects and were unable to detect any instances of severe suicidal ideations. In both groups, a very small percentage (under 10%) of subjects experienced a statistically-reliable increase in the severity of their depression. There was no difference between iCBT and OPE in this percentage, as opposed to prior studies comparing Internet-based interventions and a non-treatment (e.g., waiting list) control group, in which deterioration in depressive symptoms was more common in controls (Ebert et al., 2016a). Clearly, this discrepancy between our and prior results might be explained by our comparison of two active treatments, instead of comparing an intervention versus no intervention. Nonetheless, our findings still highlight the need for a closer look at those who use either of these two approaches — an Internet program like GET.ON Mood Enhancer or online psychoeducation — perhaps monitoring the severity of depression more frequently and offering additional support (e. g., medication and/or psychotherapy) to those who start to feel worse over the course of the intervention.

Seventeen subjects (26%) in the iCBT group attributed at least minor expressions of negative side-effects, besides worsened depression, to the intervention. Very few data have been published on potential negative effects from either Internet-based interventions or psychotherapy. However, the rate of negative side-effects reported in the present trial is much lower than in a recent study of traditional face-to-face psychotherapy in both inpatients and outpatients with major depression and co-morbid disorders, with about 70% of subjects reporting at least one negative side-effect (Abeling et al., 2017). The side-effect most frequently reported in the present trial was decreased mood during the intervention phase (Table S4). One explanation might be that CBT-based exposure exercises can evoke uncomfortable thoughts and emotions, which could adversely impact a person's mood. A negative side-effect like diminished mood could be considered a normal phenomenon during the course of any psychological intervention (Foulkes, 2010). Others indicated a fear of negative consequences when other people or institutions found out that they had participated in a depression study intervention. Additional information about Internet-based interventions and e-coaching prior to study entry might have been beneficial to enhance potential participants' beliefs in the intervention's credibility. For example, introduction videos have been shown to increase users' acceptance of Internet-based interventions and reduce barriers like the fear of stigmatization in previous studies (Ebert et al., 2015), and might be a way to reduce negative effects associated with negative expectations about the intervention.

One further potential adverse effect of Internet-based interventions might be that they are less intensive than required to treat severely-affected individuals (Kiluk et al., 2011), and that this might discourage non-responders from seeking more intensive treatments. Our subgroup analysis of participants who did not reach the criterion for a clinical response, revealed no difference in attitudes or changes in attitude toward seeking professional psychological help between those in the GET.ON Mood Enhancer and psychoeducation group. This corresponds to other research that has evaluated the impact of iCBT on help-seeking attitudes, suggesting that, even if someone fails to respond to iCBT, this does not appear to adversely impact their decision to seek other sources of help in the future (Moritz et al., 2013).

Limitations

Our study had several limitations. First, the results of our analysis indicate that past psychotherapy prior to study entry exerted a meaningful impact on the intervention's overall success. Although the statistical methods we used in analysis are presumed to be robust, with respect to baseline imbalances, our findings still must be interpreted with caution. Nonetheless, as ours is one of the first studies to include psychotherapy experiences as a potential confounder of treatment effects, our results should provide future investigators with valuable information for power calculations and analysis planning. Secondly, some participants in our iCBT group experienced a number of negative side-effects after starting the intervention. It is important to bear in mind that any negative response on one of the 15 INEP statements was counted as adverse event, independent of the intensity of the item response. Therefore, the negative side-effects derived from this measure may be overestimated. Unfortunately, at the time the study was conducted, there existed, to our knowledge, no better accurate instrument for measuring negative effects in psychotherapy. Moreover, we did not assess these negative side-effects in the online psychoeducation group. However, the findings about negative effects of the guided self-help iCBT can only be interpreted in relation to the psychoeducational control in this trial. An additional passive control condition would have been helpful to derive conclusions about the general efficacy and negative effects of both guided self-help iCBT and online psychoeducation on depression.

Conclusions

Both guided self-help Internet-based CBT and online psychoeducation appear to substantially reduce the severity of depression in patients with a Major Depressive Disorder, with the former significantly superior only immediately post treatment, but not at the follow-up. Given that satisfaction ratings were much lower for the shortened version of GET.ON Mood Enhancer in the present study compared to prior evaluations of the program, future studies should explore the comparable credibility and perceived effectiveness of the two versions. Moreover, the superiority of iCBT over online psychoeducation seems specific for those who have not had prior psychotherapy. Although we can conjecture that, perhaps, those who have had prior psychotherapy already have at least some of the knowledge and tools our iCBT program provided, further research to clarify this issue is warranted. Finally, no subject in either group reported serious suicidal ideations, and no real difference was detected between the two studied treatments with respect to other adverse effects and outcomes. Nonetheless, since a small percentage in both treatment groups did experience considerable worsening of their depression, it behooves clinicians and investigators alike to monitor individuals using these interventions closely, so such

worsening can be detected and appropriately countered.

Authors' contribution

DE, DL, and MB obtained funding for this study. JR, LB, DL, and DE contributed to the development of the GET.ON Mood Enhancer program. DE was responsible for the initial study design draft, while JR and LB contributed to the final study design. LB conducted the main data analyses. JR drafted the manuscript. DE supervised the writing process. All authors contributed to further writing of the manuscript, and all authors read and approved the final manuscript.

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All procedures involved in the study were consistent with the generally-accepted standards of ethical practice approved by the University of Marburg ethics committee (No. 2013–08 K). The trial is registered in the German clinical trials register under DRKS00005025.

Declaration of competing interests

Mr. Ebert, Mr. Lehr, and Mr. Berking hold shares of the GET.ON Institute for Online Health Training, which aims to transfer scientific knowledge related to the present research into routine mental health care in Germany. The foundation of such an institute to disseminate findings and products from the research project was the primary aim of the European Union for funding the currently-presented research. Mr. Berking has received research grants from the German Ministry of Research and the German Research Association and personal fees from various institutions providing ongoing training for psychotherapists. Mr. Ebert has received funds from the German Ministry of Research and the German Research Association, the European Union, the SVLFG and consultancy fees from Schoen Kliniken, Agaplesion Kliniken, Sanofi, Novartis, BARMER, Techniker Krankenkasse. No other disclosures are reported.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2018.12.065.

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Supplement

Table S1. Effect sizes of changes from baseline to the follow-ups between the groups on the continuous secondary outcomes based on descriptive data with multiple imputations (intention-to-treat sample).

	Baseline to 6 weeks			Baseline to 3 months		
Outcome	d[a]	CI_{low}[b]	CI_{upp}	d	CI_{low}	CI_{upp}
QIDS	0.36	0.01	0.70	0.15	-0.19	0.49
PHQ-D	0.25	-0.09	0.59	0.12	-0.22	0.46
BADS	1.16	0.79	1.53	0.70	0.35	1.05
HADS-A	0.40	0.05	0.74	0.23	-0.12	0.57
WHO5	0.47	0.12	0.81	0.44	0.10	0.79
SPSI-PPO	0.33	-0.02	0.67	0.29	-0.06	0.63
SPSI-NPO	0.30	-0.04	0.65	0.24	-0.11	0.58
SF12-PH	-0.15	-0.49	0.19	-0.07	-0.42	0.27
SF12-MH	0.39	0.05	0.74	0.24	-0.10	0.59

Abbreviations: [a]Cohen's d was calculated by standardizing differences from baseline to follow-up scores by the pooled standard deviation of the baseline scores; positive d indicates a superiority of GET.ON Mood Enhancer compared to online psychoeducation; [b]CI: 95% confidence intervals for Cohen's d; /=No assessment; HRSD=Hamilton Rating Scale for Depression; QIDS=Quick Inventory of Depressive Symptomatology - Clinician-Rating; PHQ=Patient Health Questionnaire-Depression; BADS=Behavioral Activation Depression Scale; HADS-A=Hospital Anxiety and Depression Scale – Anxiety Subscale; WHO5= World Health Organization's 5 Wellbeing Index; SPSI-PPO=Social Problem-Solving Inventory – Positive Problem Orientation; SPSI-NPO=Social Problem-Solving Inventory – Negative Problem Orientation; SF12-PH=SF-12 Health Survey – Physical Health Subdomain; SF12-MH=SF-12 Health Survey – Mental Health Subdomain.

Table S2. Estimated differences in change from baseline to six weeks and three month follow-up of secondary outcomes in each group based on mixed-effect-model including psychotherapy history, time, and its interaction as predictors.

		Intercept Baseline		Psychotherapy history		T1-T2		T1-T2 x Psychotherapy history		T1-T3		T1-T3 x Psychotherapy history	
Outcome	Condition	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE
QIDS	iCBT	10.41	0.82	2.31[b]	0.84	-3.89[a]	1.03	-0.19	1.20	-3.96[a]	1.03	-0.63	1.20
	OPE	10.76	0.70	2.32[b]	0.84	-1.39[c]	0.81	-2.11[c]	1.12	-3.16[a]	0.81	0.90[d]	1.51
PHQ-D	iCBT	15.39	0.88	0.48	0.90	-7.06[a]	1.01	2.72[b]	1.19	-6.86[a]	1.01	1.93[d]	1.19
	OPE	15.88	0.74	0.48	0.90	-3.40[a]	0.80	1.14	1.10	-4.79[a]	0-79	-0.37	1.10
BADS	iCBT	20.50	1.43	-1.65	1.47	11.10[a]	1.80	-2.19	2.10	8.94[a]	1.80	-0.77	2.10
	OPE	22.74	1.24	-1.65	1.47	2.18[d]	1.42	-0.34	1.96	3.99[b]	1.42	-0.37	1.96
HADS-A	iCBT	11.69	0.68	0.19	0.70	-4.89[a]	0.73	2.83[b]	0.87	-4.17[a]	0.73	1.83	0.87
	OPE	11.65	0.59	0.19	0.70	-1.61[b]	0.58	-0.10	0.81	-2.49[a]	0.58	0.54	0.81
WHO5	iCBT	4.95	0.76	-0.67	0.79	3.89[a]	0.92	-0.81	1.08	5.33[a]	0.92	-1.40[d]	1.08
	OPE	4.77	0.66	-0.67	0.79	2.07[d]	1.12	0.41	1.01	2.95[a]	0.73	0.40	1.01
SPSI-PPO	iCBT	7.60	0.71	-0.09	0.73	2.37[b]	0.72	-0.10	0.83	2.34[b]	0.73	-0.31	0.83
	OPE	7.74	0.61	-0.09	0.73	1.06[c]	0.55	0.01	0.77	0.93[d]	0.55	0.15	0.77
SPSI-NPO	iCBT	8.02	0.83	0.68	0.85	-1.88[c]	0.89	0.60	1.06	-1.75[c]	0.89	0.18	1.36
	OPE	7.91	0.71	-0.21	0.98	0.07	0.70	0.80	1.36	0.02	0.70	-1.08	0.98
SF12-PH	iCBT	44.81	1.80	-0.29	1.85	0.27	1.84	-2.53	2.19	0.94	1.84	-1.74	2.18
	OPE	46.40	1.55	-0.29	1.85	0.19	1.46	-1.36	2.04	-0.71	1.46	1.82	2.04
SF12-MH	iCBT	26.90	1.65	-0.39	1.70	9.84[a]	2.13	-2.25	2.49	11.79[a]	2.13	-2.10	2.49
	OPE	26.85	1.43	-0.39	1.70	6.03[a]	1.70	-1.95	2.33	8.41[a]	1.70	-0.06	2.33

Abbreviations: HRSD=Hamilton Rating Scale for Depression; QIDS=Quick Inventory of Depressive Symptomatology - Clinician-Rating; PHQ=Patient Health Questionnaire-Depression; BADS=Behavioral Activation Depression Scale; HADS-A=Hospital Anxiety and Depression Scale – Anxiety Subscale; WHO5= World Health Organization's 5 Wellbeing Index; SPSI-PPO=Social Problem-Solving Inventory – Positive Problem Orientation; SPSI-NPO=Social Problem-Solving Inventory – Negative Problem Orientation; SF12-PH=SF-12 Health Survey – Physical Health Subdomain; SF12-MH=SF-12 Health Survey – Mental Health Subdomain; iCBT=Internet-based cognitive behavior therapy; OPE=online psychoeducation on depression; [a]=$p<0.001$; [b]=$p<0.01$; [c]=$p<0.05$; [d]=$p<0.10$.

Table S3. Estimated group differences of secondary outcomes based on mixed-effect-model including two- and threefold interaction terms with group, time, and history of psychotherapy as predictors.

	Group Baseline		T1-T2 x Group				T1-T2 x Psychotherapy history x Group				T1-T3 x Group				T1-T3 x Psychotherapy history x Group			
Outcome	B	SE	B	SE	CI_{low}	CI_{upp}	B	SE	CI_{low}	CI_{upp}	B	SE	CI_{low}	CI_{upp}	B	SE	CI_{low}	CI_{upp}
QIDS	-0.35	0.83	-2.50[b]	1.25	-4.96	0.04	1.92	1.51	-1.04	4.88	-0.80	1.25	-3.26	1.66	0.90	1.51	-2.06	3.87
PHQ-D	-0.44	0.89	-3.66[b]	1.24	-6.10	-1.22	3.86[b]	1.52	0.87	6.84	-2.08[c]	1.24	-4.52	0.36	2.30[d]	1.52	-0.68	5.29
BADS	-2.25[d]	1.45	8.92[a]	2.19	4.61	13.23	-1.85	2.64	-7.04	3.33	4.95[c]	2.19	0.64	9.26	-0.40	2.64	-5.59	4.78
HADS-A	0.04	0.69	-3.27[a]	0.91	-5.06	-1.49	2.93[b]	1.12	0.73	0.51	-1.68[c]	0.91	-3.46	0.10	1.30	1.12	-0.90	3.49
WHO5	0.18	0.77	2.07[c]	1.13	-0.15	4.29	-1.22	1.36	-3.91	1.46	2.38[c]	1.13	0.16	4.60	-1.80[d]	1.36	-4.49	0.88
SPSI-PPO	-0.14	0.72	1.31[d]	0.87	-0.40	3.02	-0.11	1.08	-2.24	2.02	1.40[d]	0.87	-0.31	3.11	-0.46	1.08	-2.60	1.67
SPSI-NPO	0.11	0.84	-1.95[c]	1.10	-4.12	0.22	0.80	1.36	-1.87	3.48	-1.77[d]	1.10	-3.94	0.40	1.27	1.36	-1.41	3.94
SF12-PH	-1.59	1.82	0.07	2.28	-4.42	4.57	-1.17	2.83	-6.74	4.39	1.66	2.28	-2.84	6.15	-3.56	2.83	-9.13	2.00
SF12-MH	0.05	1.67	3.81[d]	2.59	-1.29	8.97	-0.30	3.09	-6.38	5.79	3.37[d]	2.59	-1.73	8.48	-2.03	3.09	-8.11	4.05

Abbreviations: HRSD=Hamilton Rating Scale for Depression; QIDS=Quick Inventory of Depressive Symptomatology - Clinician-Rating; PHQ=Patient Health Questionnaire-Depression; BADS=Behavioral Activation Depression Scale; HADS-A=Hospital Anxiety and Depression Scale – Anxiety Subscale; WHO5= World Health Organization's 5 Wellbeing Index; SPSI-PPO=Social Problem-Solving Inventory – Positive Problem Orientation; SPSI-NPO=Social Problem-Solving Inventory – Negative Problem Orientation; SF12-PH=SF-12 Health Survey – Physical Health Subdomain; SF12-MH=SF-12 Health Survey – Mental Health Subdomain; iCBT=Internet-based cognitive behavior therapy; OPE=online psychoeducation on depression; [a]=$p<0.001$; [b]=$p<0.01$; [c]=$p<0.05$; [d]=$p<0.10$.

Table S4. Negative Side-Effects from the intervention.

No.	Statement of the INEP[a]	n[b]	%
1	Since completing the training I feel worse.	1	1.5
2	Since the end of the training it is hard for me to trust others than it was before.	0	0
3	Since completing the training I have suffered more from past events than I did before.	5	7.7
4	Since completing the training I experience more conflicts with my partner than before.	4	6.2
5	Since completing the training my relationship with my family is worse than before.	1	1.5
6	Since completing the training my relationships with my friends is worse than before.	1	1.5
7	Since the beginning or after completing this training, I worry that my classmates/colleagues/fellow students may find out that I participated in this study	3	4.6
8	During the training or since completing the training I got in trouble regarding my insurances or I fear that problems may appear in the future.	4	6.2
9	During the training or since completing the training I worry more about financial problems than before.	0	0
10	During the training or since completing the training I felt dependent on my e-Coach.	3	4.6
11	During the training or since completing the training I struggle more with making my own decisions	2	3.1
12	My partner was jealous of my relationship with my e-Coach.	0	0
13	During the training or since completing the training there were phases I was feeling mentally unwell.	6	9.2
14	During the training or since completing the training I have changed for the worse.	2	3.7
15	During the training or since completing the training I have had, for the first time, suicidal thoughts	0	0

Abbreviations: [a]INEP= Inventory for the Assessment of Negative Effects of Psychotherapy; [b]Multiple choices made by 17 out of 65 participants in the intervention group.

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Efficacy and moderators of psychological interventions in treating subclinical symptoms of depression and preventing major depressive disorder onsets: protocol for an individual patient data meta-analysis of randomised controlled trials

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ABSTRACT

Introduction The long-term effectiveness of psychological interventions for the treatment of subthreshold depression and the prevention of depression is unclear and effects vary among subgroups of patients, indicating that not all patients profit from such interventions. Randomised clinical trials are mostly underpowered to examine adequately subgroups and moderator effects. The aim of the present study is, therefore, to examine the short-term and long-term as well as moderator effects of psychological interventions compared with control groups in adults with subthreshold depression on depressive symptom severity, treatment response, remission, symptom deterioration, quality of life, anxiety and the prevention of major depressive disorder (MDD) onsets on individual patient level and study level using an individual patient data meta-analysis approach.

Methods and analysis Systematic searches in PubMed, PsycINFO, Embase and the Cochrane Central Register of Controlled Trials were conducted. We will use the following types of outcome criteria: (A) onset of major depression; (B) time to major depression onset; (C) observer-reported and self-reported depressive symptom severity; (D) response; (E) remission; (F) symptom deterioration; (G) quality of life, (H) anxiety; and (I) suicidal thoughts and behaviours. Multilevel models with participants nested within studies will be used. Missing data will be handled using a joint modelling approach to multiple imputation. A number of sensitivity analyses will be conducted in order test the robustness of our findings.

Ethics and dissemination The investigators of the primary trials have obtained ethical approval for the data used in the present study and for sharing the data, if this was necessary, according to local requirements and was not covered from the initial ethic assessment. This study will summarise the available evidence on the short-term and long-term effectiveness of preventive psychological interventions for the treatment of subthreshold depression and prevention of MDD onset. Identification of subgroups of patients in which those interventions are most effective will guide the development of evidence-based personalised interventions for patients with subthreshold depression.

Strengths and limitations of this study

- A strength of the presented individual patient data meta-analysis (IPD-MA) is that this approach allows sufficient statistical power to evaluate specific effects for specific kinds of treatments for patients with certain characteristics, in order to select the best possible treatment for an individual patient (ie, personalised medicine).
- One limitation of the IPD-MA is that while investigating moderators of treatment outcome, one very much relies on the variables that have been assessed in the primary studies. However, many of the relevant predictors and moderators associated with depression onset or differential treatment response reported in the literature were not assessed in the included studies.
- Another limitation of the IPD-MA approach is that some bias is introduced because not all eligible trials can be included in the analyses due to author non-response, lack of ethical approval to share the data or that data are not available anymore.

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INTRODUCTION

Major depressive disorder (MDD) is highly prevalent,[1–4] associated with substantial impairment[5 6] and economic costs.[7–9] Psychological treatments have been shown to be effective in the treatment of depression.[10 11] However, it has been estimated that even under the hypothetical scenario of full coverage with and adherence to evidence-based treatments, approximately only one-third of the disease burden attributable to MDD could be averted.[12] Moreover, in practice, the majority

of depressed people remain untreated,[3 13] even in high-income countries.[14 15]

Therefore, attention has increasingly been shifted to the prevention of MDD onsets.[16 17] One specific form of prevention is indicated prevention. In such interventions, subthreshold symptoms are treated in order to prevent the transition to a full-blown depressive disorder.[17] Meta-analytic evidence shows that indicated psychological preventive approaches can be effective in preventing depressive episodes.[18] The latest systematic review, which included randomised trials that have been published up to March 2012, found psychological interventions for subclinical symptoms to be effective in reducing the risk of developing an MDD at 6-month (incidence rate ratio (IRR)=0.61; 5 studies) and 12-month follow-up (IRR=0.74; 4 studies). Since then, many more randomised controlled trials (RCT) have been published, warranting an update of the evidence.

Moreover, the treatment of subclinical symptoms of depression itself is relevant. Subthreshold depressive symptoms are highly prevalent,[19] related to increased mortality,[20] poorer quality of life,[21] increased healthcare service utilisation[22] and vast economic costs.[23] However, results for the treatment of subclinical symptoms are yet conflicting. Pharmacological interventions are unlikely to have a clinical advantage over placebos in treating subthreshold depression.[24] In addition, although a recent meta-analysis found small-to-moderate effect sizes for psychological interventions on depressive symptom severity at post-treatment compared with usual care,[25] four studies using clinician-rated outcomes did not indicate significant positive results.[25] Moreover, we are not aware of any systematic review exploring the long-term effects of treatments for subclinical symptoms with regard to depressive symptom severity, and effects on other relevant outcomes such as anxiety or quality of life have not been examined.

Another issue not yet addressed is the possibility that the effectiveness of psychological interventions for subthreshold depression varies across patients and not all subgroups of patients profit from such interventions. Given that the number of people from specific subgroups is often small in single trials, and randomised trials are usually powered to detect overall treatment effects, RCTs are mostly underpowered to perform adequately subgroup and moderator analyses.[26] As studies also seldom report effectiveness for different patient characteristics, it is impossible to examine patient-level moderators using traditional meta-analytic approaches.

Individual participant data meta-analyses (IPD-MA) can overcome some of the limitations of the conventional meta-analyses on study level.[27–29] By pooling the primary data of individual trials, it is possible to conduct analyses not reported in original studies and obtain large enough sample sizes with sufficient power to examine the effects in relevant subgroups and identify outcome moderators.[30]

The present study aims to examine the short-term and long-term effects of psychological interventions compared with control groups in adults with subthreshold depression on depressive symptom severity, treatment response, remission, symptom deterioration, quality of life, anxiety and the prevention of MDD onsets using an IPD-MA approach. Moderators on individual patient level (eg, sociodemographic, clinical characteristics) and study level (eg, type of treatment delivery, number of sessions, theoretical basis) on intervention outcome will be explored in the pooled data set. In addition, we will analyse the intervention effects and moderators of effects in specific subgroups of interest (eg, using only data from patients with low education, chronic medical conditions, and so on).

METHOD

General study approach

First, a systematic review is performed to identify eligible papers. Corresponding authors of selected studies will be contacted and asked to provide raw data from their studies. The current study will be completed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. IPD will be aggregated and a priori defined moderator variables will be analysed using a multilevel model approach.

Eligibility criteria

In this IPD-MA, we will (A) include randomised trials in which (B) the effects of a psychological treatment (delivered individually, in a group-based, bibliotherapy, internet-based format) were compared with a comparison group (waiting list, care as usual, psychological placebo, pill placebo, antidepressant medication) (C) in adults (D) with clinically relevant depressive symptoms (E) but no MDD at baseline, (F) assessed with a standardised diagnostic interview (see below) to exclude participants with full-blown mood disorder at baseline. Psychological interventions are defined as the application of psychological mechanisms and interpersonal stances derived from psychological principles for the purpose of assisting people to modify their behaviours, cognitions, emotions and/or other personal characteristics in directions that the participants deem desirable.[31 32] Clinically relevant depressive symptoms will be defined as scoring above a cut-off score on a self-rating depression questionnaire; scoring above a cut-off score on a clinician-rated instrument; or meeting criteria for minor depression according to the Diagnostic and Statistical Manual of Mental Disorders, or the International Classification of Diseases. We will also include studies in which participants with a diagnosed depressive disorder were examined and we will then exclude participants with a full-blown disorder on an individual basis using the primary data. No language restrictions will be applied.

Types of outcome measures

We will use the following types of outcome criteria: (A) onset of MDD; (B) time to MDD onset; (C)

observer-reported and self-reported depressive symptom severity; (D) response; (E) remission; (F) symptom deterioration; (G) quality of life; (H) anxiety; and (I) suicidal thoughts and behaviour. MDD will be assessed with clinical interviews such as the Structured Clinical Interview for DSM Disorders,[33] the Composite International Diagnostic Interview,[34] or the Mini-International Neuropsychiatric Interview.[35] Depressive symptom severity will be measured using standardised depression outcome measures such as the Beck Depression Inventory,[36] Hamilton Depression Rating Scale,[37] or the Center for Epidemiological Depression Scale.[38] If both observer-rated and self-report measures are available, we will explore intervention effects on both outcome measure types. If several observer-rated or self-report measures are used, preference will be given to the mostly used measures across the different studies in order to increase comparability. If the type of outcome measures varies between studies, these measures will be transformed into standardised scores (using the common metric approach[39] or, if this is not possible, z-transformation). We will also dichotomise scores on depressive symptoms to explore the effects on two response criteria (a 50% reduction in symptoms for relative change; a minimum absolute change in symptoms according to the Reliable Change Index)[40] and remission (scoring below a predefined cut-off score). Symptom deterioration rates will be calculated using a predefined absolute worsening of symptoms from baseline to follow-up using the Reliable Change Index[39] and 50% symptom increase. Quality of life will be transformed to quality-adjusted life-years using, if possible, the British value set for EQ-5D-3L utility values[41] and Brazier's algorithm for SF-6D utility values,[42] respectively. Anxiety severity will be measured using standardised self-report measures, such as the Hospital Anxiety and Depression Scale[43] or Beck Anxiety Inventory.[44] Note that we are planning to reduce the complexity for moderator analyses by only focusing on (A) onset of MDD and (C) depressive symptom severity.

Moderators

We will investigate both moderators on individual patient level (eg, sociodemographic, clinical characteristics) as well as on study level (eg, type of treatment delivery, number of sessions, theoretical basis). Published papers are examined to identify potential moderators on patient level that have been assessed across studies. We will explore variables that have shown to predict differential treatment outcome in psychological treatments for depression[45 46] and variables that are associated with depression onset.[47–49]

Clinical and personality characteristics that shall be investigated include depressive symptom severity,[50] lifetime history of MDD,[51 52] number of previous depressive episodes,[51 53] anxiety symptoms,[51] comorbid mental health disorder (eg, anxiety disorder),[52] previous exposure to depression treatment, family history of common mental health disorders,[52 54 55] global assessment of functioning, sleeping problems,[56–58] neuroticism,[50] recent life stress,[59] childhood adversities,[55] traumatic events,[60] significant life events (in the previous year),[61 62] daily hassles, emotion regulation,[63] poor self-perceived health (quality of life),[51 56 62] self-esteem,[64–66] (chronic) medical conditions,[57 58 67] physical functioning/disability,[56] mastery, worrying, body mass index, rumination, interpersonal problems,[53 62] body dissatisfaction,[66 68] physical activity level,[56 69] diet quality,[69] alcohol/substance use,[52 56 62] smoking,[56 67] resilience,[70] social support/integration[52 57 63 66] and perceived social rejection/mobbing. Sociodemographic variables that shall be examined include sex,[54 67 71 72] age,[52 71] education,[58 73] marital status,[73] relationship status,[71] living alone,[55] employment,[55] ethnicity (minority status),[74] economic deprivation/poverty[57 62 74] and parenthood (motherhood).[67] It is expected that not all studies that will be included will assess all variables. Hence, a precondition for including a variable as a moderator in the actual analyses is availability of sufficient data. Intervention characteristics that will be examined include the intervention format (individual, group or guided self-help), the number of treatment sessions, overall treatment duration, session frequency,[75] the type of delivery (internet, face-to-face), the control condition (placebo/attention control, care as usual, waitlist, alternative treatment), type of psychotherapy (cognitive behavioural therapy, problem-solving, interpersonal or other type) and study quality.

Timing of outcome assessments

All postintervention assessments will be pooled and treated as one assessment, despite varying time frames in included studies. Treatment duration will be controlled for if found to be associated with the dependent variable. We expect varying follow-up periods of the studies and will therefore categorise follow-ups into meaningful categories, such as follow-up that occurred 3–7 months (follow-up I), 8–13 months (follow-up II) or over 14 months (follow-up III) after baseline.

Searches and study selection

For the identification of potential studies for inclusion, we will use a database of papers on the psychological treatment of depression described in detail elsewhere.[76] For this database, studies have been identified from PubMed, PsycINFO, Embase and the Cochrane Central Register of Controlled Trials. In addition, previous meta-analyses of treatments for depression were screened for this database to ensure that no randomised trial was missed. These searches identified a total of 16 407 abstracts (12 196 after the removal of duplicates); from this, 1885 full-text papers of RCTs on treatments for depression were retrieved for possible inclusion in the database. These papers will be screened for inclusion in this meta-analysis. A further literature search will be conducted for studies published since the last update of the database (studies published up to December 2017 will be considered for inclusion). In addition, relevant authors in the field of depression

prevention will be asked whether they are aware of any yet unpublished study that might fit the inclusion criteria.

Corresponding authors will be contacted for each of the identified papers and will be asked to provide raw data from their study. If an author does not respond after 1 month, a second attempt to contact him/her will be made. If the second contact fails, another author of the study will be contacted and invited to participate. A second attempt to contact this author will follow a month later if no response is received, and so forth, until a maximum of three authors were contacted. Study data will be considered unavailable in the event that no study author has responded to multiple contact attempts or if all contacted authors indicate that they no longer have access to the data. If authors do not respond, are not able or not willing to share their data, we will compare these studies with the included ones in terms of design, participants, intervention and quality.

Risk of bias assessment

The validity of the included studies will be assessed using four criteria from the Cochrane 'Risk of Bias' assessment tool.[77] This tool identifies possible sources of bias, including the adequate generation of allocation sequence, the allocation concealment, blinding of assessors and dealing with incomplete outcome data (this is assessed as positive when intention-to-treat analyses were conducted, meaning that all randomised participants were included in the analyses). Only data from published papers will be used to determine the risk of bias in order to use a consistent procedure across studies that does or does not share data. Two researchers will conduct the quality assessment independently and agreement rates will be reported. Disagreement will be solved through discussion.

Missing data

IPD-MA will be conducted according to the intention-to-treat principle. Missing data are handled using a joint modelling approach to multiple imputation of IPD nested within studies.[78–80] In particular, we will use the R package jomo that uses Markov chain Monte Carlo techniques to draw replacements for the missing values.[81] This procedure is based on a multilevel imputation model that considers associations between continuous and categorical variables both at the level of participants (level 1) and studies (level 2). In addition, it allows for modelling between-study heterogeneity in the covariance matrices, which is especially useful when imputing variables that are completely missing from studies.[78] We will specify a multivariate empty imputation model including all available participant (level 1) and study (level 2) characteristics.[82] Assignment to intervention group versus control group will be used as a grouping variable in the imputation model to allow for treatment-specific intercept, variance and covariance parameters. Based on the final model, we will generate at least 20 imputed data sets. The number of burn-in iterations and the number of iterations between imputed data sets will be chosen so that convergence can be ensured.[82] In the case of persistent convergence problems, we will reduce the number of model parameters by dropping predictors and/or imposing constraints to the model (eg, assuming a common level 1 covariance matrices across studies).

Analysis

Conventional meta-analysis on study level

We will first conduct a conventional meta-analysis using data from the published papers. This will enable us to examine whether studies that did not provide data might bias the results of our IPD-MA. This will be done by comparing those studies contributed to the IPD data set with those who did not with regard to the outcomes, risk of bias and other study characteristics.

First, we will calculate the IRR for developing a depressive disorder in the intervention compared with the control group for each study based on published papers, and then pool the results using the Comprehensive Meta-Analysis Software package V.3. With regard to effects on depressive symptom severity, we will calculate Hedges' g as a measure of the effect size indicating the difference between the intervention and control conditions at post-treatment. These analyses will be done using a random effects DerSimonian-Laird model[83] because considerable heterogeneity between studies is expected. To test the homogeneity of effect sizes, we will calculate the I^2 statistic as an indicator of heterogeneity in percentages.[82] A value of 0%–40% indicates unimportant heterogeneity, and larger values indicate increasing heterogeneity, with 30%–60% as moderate, 50%–90% substantial and 75%–100% as considerable. We will calculate 95% CIs using the non-central X^2-based approach.[84] Small sample bias will be tested by inspecting the funnel plot visually, the Egger's test, and Duval and Tweedie's trim-and-fill procedure,[85] which yields an estimate of the effect size after small sample bias has been taken into account.[86]

Individual participant data meta-analysis

For the IPD-MA, we will use a one-step data analysis approach. This is currently the best possible meta-analysis approach with the standard two-step analysis being at best equivalent in some scenarios.[87] All models are repeated for all of the defined follow-ups.

Effects on MDD onset

We will use multilevel logistic regression analysis based on the imputed data sets for predicting the occurrence of MDD, including the assignment to intervention group versus control group as the focal predictor. Patient-level data will be treated as level 1 and study-level data as level 2. Models will include both random intercepts and random slopes to capture both unobserved heterogeneity in trial populations (intercept) and trial effectiveness (slope). We will calculate ORs and corresponding 95% CIs, and then calculate the numbers needed to treat (NNT) and

corresponding 95% CIs in order to avoid one additional MDD. In addition, we will conduct two additional analyses taking varying observation periods and time to MDD onset explicitly into account. To control for differences in observation periods, we will use a multilevel binomial regression analysis with a complementary log-log link and offset for time since baseline, which provides an estimate of the treatment effect in terms of the IRR for developing an MDD.[88] To assess the differences in time to MDD onset, we will use multilevel Cox proportional hazards models, which provide an estimate of the treatment effect in terms of the HR for developing an MDD.

Effects on symptom severity

We will predict standardised depressive symptom severity scores from intervention group versus control group and control for baseline depressive symptom severity using a multilevel linear regression analysis. Again, we will include both a random intercept and a random slope for treatment effects to capture both unobserved heterogeneity between study populations (intercept) and study effectiveness (slope). Hedges' g will be calculated as an effect size measure. The same approach will be used for analysing effects on other continuous outcome measures including quality of life and anxiety and suicidal ideation.

Effects on response, remission and symptom deterioration

The standard criterion for measuring response in psychotherapy outcome research for depression is a 50% reduction on a standardised depression measure.[89] However, it can be argued that in individuals with subclinical symptoms a relative reduction of 50% of symptoms might be clinically less meaningful compared with individuals with major depression. Hence, we will additionally calculate response using a predefined absolute reduction in symptoms using the Reliable Change Index.[40] Remission will be defined using standard cut-off scores of the respective instruments. Symptom deterioration will be defined using a predefined absolute worsening of symptoms from baseline to follow-up using the Reliable Change Index[40] and 50% symptom increase. Generally, event occurrence will be predicted from treatment group using multilevel logistic regression analysis. We will proceed to calculate the OR and its 95% CIs, and then calculate the NNT and its 95% CIs in order to achieve one additional response, respectively remission as compared with the control group.[90]

Moderator analyses

We will explore predictors of outcome (ie, prognostic variables) and moderators of the intervention effect (ie, prescriptive variables) by including selected participant-level and study-level variables as well as their interactions with the intervention as additional predictors in the multilevel (logistic) regression analyses. These analyses will be based on the total sample (ie, on the imputed data sets including all studies) and focus on predicting onset of MDD, depressive symptom severity and symptom deterioration. Variables will be selected based on the combination of multiple criteria, including the amount of available/missing data, the bivariate associations with outcome measures in the intervention group and control group, and the convergence of the multiple imputation model. In order to increase statistical power, moderator analyses on long-term effects will be done using combined follow-up assessments to include all studies that contribute follow-up data.

Subgroup analyses

We also plan to examine the effectiveness of the interventions and moderators of treatment outcome in subgroups that are of special interest for tailoring prevention programmes (eg, older adults, low-educated adults, minority status, mothers of newborns, medical conditions and individuals without lifetime history of depression). These analyses will be based on subsamples. Note that it will be necessary to generate new imputed data sets for these analyses to ensure congeniality with the imputation model.[80] The same strategy will be applied to investigate effects and moderators in specific intervention delivery forms (eg, internet, guided/unguided self-help, group format). However, whether these and other analyses in subgroups of interest should be conducted depends on the number of studies/participants that are eligible.

Sensitivity analyses

A number of sensitivity analyses will be conducted in order to test the robustness of our findings. For example, we will run a separate model in which we exclude trials with high risk of bias. If a sufficient number of studies include the same outcome measurement (eg, for depressive symptom severity), we will conduct separate analyses using only this specific outcome measurement, instead of using the standardised score. We will also run a complete case analysis and compare the results with the intention-to-treat analysis in order to determine whether a difference exists between those that dropped out from the trials compared with those who persisted. Other sensitivity analyses may be necessary and will be decided on after all data have been collected and examined.

DISCUSSION

The burden attributable to major depression is immense and although effective treatments are available, effects on disease burden are limited. Treatments so far failed to show that the prevalence of depression in the population can be reduced, even in those countries in which evidence-based treatments have been made widely available. Hence, new approaches are needed to reduce the burden of MDD at population level. This study will provide a precise estimate of the effects of indicated preventive interventions for subclinical symptoms of depression on short-term and long-term depressive symptom severity, MDD onset and other relevant outcome criteria. Using an IPD meta-analytic approach, we will be able to estimate

specific effects in relevant subgroups of interest and test whether the effectiveness depends on individual participant criteria.

Such approaches have been used with some frequency in medicine, but are less often applied in the field of psychological treatment outcome research, although recently a number of studies have been published[91–97] or are in preparation.[98–100] As the field moves towards personalised medicine, it is crucial to know specific effects for specific kinds of treatments for patients with certain characteristics in order to select the best possible treatment for an individual patient. IPD-MA allows to do this with sufficient statistical power.

However, such an approach also has a number of challenges. First, until such a study is published, it is very likely that the search is already outdated and more trials have already been published that could theoretically have been included. This is due to the fact that solely the process of obtaining and integrating primary data into one data set takes very long. Updating the search and including additional data sets within the review process needs to be balanced to what can be gained by doing so with regard to the specific research question investigated, as theoretically this process could be done repeatedly. For example, if effects in relevant investigated subgroups are consistent across trials, heterogeneity is low, the number of included studies and participants is reasonable, effects are clinically meaningful with narrow CIs for effect sizes, then it is unlikely that the inclusion of an additional study would result in meaningful changes that would justify the delay in publishing the results to be available for the scientific community and policymakers. On the other hand, if differences of effect sizes between specific subgroups are substantial, but moderator analyses are underpowered to detect such a difference and the inclusion of additional studies would change this, the additional value of updating the data set would potentially outweigh the disadvantages. Second, a limitation of the IPD-MA approach is that one very much relies on the variables that have been assessed in the primary study. In addition, many relevant predictors and moderators associated with depression onset or differential treatment response in the literature, such as, for example, lifetime history of depression, childhood adversities are not included in many of the published studies. However, recent advantages in statistics allow to account for between-study heterogeneity when imputing missing values and to impute variables that are systematically missing in studies.[78 101] Nevertheless, we argue that authors should include variables in primary studies that might eventually explain heterogeneity of treatment effects, even when the study is not powered to reliably investigate differential treatment effects. This would allow using these data in IPD-MA studies and might bring the field of precision medicine in psychological treatment outcome research substantially forward. Third, another challenge with IPD-MA is that often not all available trials can be included in the data set due to author non-response, lack of ethical approval to share the data or that data are not available anymore. This might introduce some bias, which is being addressed by comparing IPD findings with those of traditional meta-analyses in the present study.

Ethics and dissemination

This paper is a study protocol for an individual patient data meta-analysis and does not require ethical approval. The investigators of the primary trials have obtained ethical approval for the data used in the present study and for sharing the data, if this was necessary, according to local requirements and was not covered from the initial ethic assessment. Only anonymised data are included in the data set which does not allow the identification of individual trial participants. Anonymised data collected are managed by CB and JAR and will be available for the complete research team. External research can request access to the data set for secondary analyses after publication of the results specified in this protocol, if local requirement of the original data should allow this.

This study will summarise the available evidence on the short-form and long-term effectiveness of preventive psychological interventions for the treatment of subthreshold depression and prevention of MDD onset. Identification of subgroups of patients in which those interventions are most effective will guide the development of evidence-based personalised interventions for patients with subthreshold depression.

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Efficacy and moderators of psychological interventions in treating subclinical symptoms of depression and preventing major depressive disorder onsets: protocol for an individual patient data meta-analysis of randomised controlled trials

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Efficacy and Moderators of Internet-Based Interventions in Adults with Subthreshold Depression: An Individual Participant Data Meta-Analysis of Randomized Controlled Trials

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Keywords
Individual participant data meta-analysis · Moderators · eHealth · Online therapy · Subclinical depression · Minor depression

Abstract
Introduction: Evidence on effects of Internet-based interventions to treat subthreshold depression (sD) and prevent the onset of major depression (MDD) is inconsistent. ***Objective:*** We conducted an individual participant data meta-analysis to determine differences between intervention and control groups (IG, CG) in depressive symptom severity (DSS), treatment response, close to symptom-free status, symptom deterioration and MDD onset as well as moderators of intervention outcomes. ***Methods:*** Randomized con-

Trial registration: PROSPERO database, registration No. CRD42017058585.

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trolled trials were identified through systematic searches via PubMed, PsycINFO, Embase and Cochrane Library. Multilevel regression analyses were used to examine efficacy and moderators. ***Results:*** Seven trials (2,186 participants) were included. The IG was superior in DSS at all measurement points (posttreatment: 6–12 weeks; Hedges' g = 0.39 [95% CI: 0.25–0.53]; follow-up 1: 3–6 months; g = 0.30 [95% CI: 0.15–0.45]; follow-up 2: 12 months, g = 0.27 [95% CI: 0.07–0.47], compared with the CG. Significantly more participants in the IG than in the CG reached response and close to symptom-free status at all measurement points. A significant difference in symptom deterioration between the groups was found at the posttreatment assessment and follow-up 2. Incidence rates for MDD onset within 12 months were lower in the IG (19%) than in the CG (26%). Higher initial DSS and older age were identified as moderators of intervention effect on DSS. ***Conclusions:*** Our findings provide evidence for Internet-based interventions to be a suitable low-threshold intervention to treat individuals with sD and to reduce the incidence of MDD. This might be particularly true for older people with a substantial symptom burden.

Introduction

Subthreshold depression (sD) is highly prevalent [1], associated with poorer quality of life [2], a higher risk of developing major depression (MDD) [3, 4], increased mortality [5] and increased use of health care services [6], as well as immense economic costs [7].

Although a meta-analysis on Internet-based interventions to treat sD found small-to-moderate effects for psychological interventions on depressive symptom severity (DSS) after treatment compared to treatment as usual [8], uptake rates of preventive interventions are low [9]. Internet-based interventions might overcome some of the barriers associated with traditional mental health care services, e.g., living in underserved areas, and fear of negative social consequences [10, 11]. Meta-analyses have shown positive effects of Internet-based interventions for depression [12, 13], with the National Institute for Health and Care Excellence guidelines recommending such interventions as a treatment option in the management of subthreshold persistent depressive symptoms and mild to moderate depression [14].

Several studies have investigated the efficacy of Internet-based interventions for the treatment of sD and the prevention of MDD. Three meta-analyses summarizing these studies found significant improvements in DSS after treatment with small to moderate effect sizes (standardized mean difference [SMD] = 0.25, 95% confidence interval, CI: 0.09–0.41 [15]; SMD = 0.28, 95% CI: 0.14–0.42 [16]; SMD = 0.35, 95% CI: 0.12–0.57 [17]). However, statistical comparisons based on group means provide limited information about clinical significance on an individual level, such as treatment response and symptom-free status [18]. In addition, evidence on the long-term efficacy remains inconsistent, with some randomized controlled trials (RCTs) showing a superiority of Internet-based programs over control conditions at follow-up [19–21], while others did not [22–24]. With regard to the prevention of MDD onset, evidence is scarce but promising with hazard ratios ranging from 0.22 (95% CI: 0.06–0.75 [25]) to 0.59 (95% CI: 0.42–0.82 [21]). Moreover, research on negative outcomes, such as symptom deterioration, in the treatment of sD is rare but of high clinical relevance [26].

However, due to insufficient power in single RCTs [27], there is little evidence on whether all subgroups of participants with sD benefit from Internet-based interventions. Moderator analyses could identify different outcome patterns between participants and provide a basis for choosing the best fitting intervention for a given individual [28]. By pooling raw data of individual trials (e.g., individual participant data meta-analysis, IPD-MA), it is feasible to perform analyses not reported in original studies and to obtain sample sizes with sufficient power to investigate effects in relevant subgroups and explore intervention and participants' characteristics as moderators of intervention outcome [29].

The aim of the present study was thus to investigate the short- and long-term effects of Internet-based interventions in comparison to control groups like treatment as usual or waiting list groups in adults with sD on DSS, treatment response, close to symptom-free status, symptom deterioration and depression onset as well as moderators on the individual and study level, using an IPD-MA approach.

Materials and Methods

Registration and Study Protocol

This IPD-MA was registered in the PROSPERO register (CRD42017058585). It was conducted and reported according to methodological guidelines for IPD-MA [30, 31]. Further details of the study can be found in the published study protocol about the planned IPD-MA on interventions for the treatment of sD and prevention of MDD [32]. Deviations from the protocol can be found in online supplement 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000507819).

Eligibility Criteria/Identification and Selection of Studies

We included RCTs in which effects of an Internet-based psychological intervention were compared with a comparison group in adults with no MDD at baseline according to DSM/ICD criteria (assessed with a standardized diagnostic categorical assessment, either via interview or self-administered questionnaire) and scoring above a cut-off on a self-rating depression questionnaire or meeting criteria for minor depression according to the Diagnostic and Statistical Manual of Mental Disorders (DSM). RCTs with mixed sD/MDD samples were included and MDD cases at baseline were removed from the data set. Studies were excluded if they were not published in English, German, Spanish or Dutch.

To identify potential studies, we used a database of articles on the psychological treatment of depression, which is described in detail elsewhere [33]. This database contains studies that have been identified using PubMed, PsycINFO, Embase and the Cochrane Central Register of Controlled Trials. In addition, previous meta-analyses on depression prevention and treatment of sD [16, 17] were reviewed, and renowned authors in the field of depression prevention were asked if they were aware of any other relevant study to ensure that no RCT was overseen. Studies published until May 30, 2017, were considered for inclusion.

Data Collection, Extraction and Preparation

Authors of eligible articles were contacted for permission to use their data sets. Reminders were sent after 2 weeks and if necessary after 1 month. In case of non-response, we excluded the trial. Authors were asked to provide data on sociodemographic, clinical and intervention-related characteristics. Potential moderators on participant level were identified by exploring variables that have been found to predict long-term outcome in depression [34, 35]. Next, moderators were extracted from studies according to the amount of available/missing data and the bivariate associations with outcome measures in the intervention and control group. Detailed information can be found in online supplement 2. Finally, we combined all individual data sets into a merged data set, using a generic standardized protocol for integrating IPD sets [36]. All postintervention assessments were pooled and treated as one assessment. Follow-ups were categorized into appropriate categories (FU1: 3–6 months, FU2: 12 months).

Risk of Bias Assessment

The validity of the included studies was assessed using four criteria from the Cochrane Risk of Bias assessment tool [37] including adequate generation of allocation sequence, allocation concealment, blinding of assessors and dealing with incomplete outcome data (e.g., intention-to-treat analyses were assessed as positive). For this assessment only the information which was actually reported in the papers was used, to ensure a consistent procedure across studies and to reduce the risk of bias based on what was reported and what was not. The quality assessment was carried out independently by two researchers (C.B., J.R.). Disagreements were resolved by discussion.

Missing Data

The IPD-MA was conducted according to the intention-to-treat principle. Missing data were handled using a fully conditional specification approach to multiple imputation using the R package mice [38]. The imputation procedure was set up in such a way that it would incorporate the nested structure of the data with individual participant data nested within studies, include all available individual and study level characteristics as predictors of missing data and allow for heterogeneity in treatment effects across studies as well as treatment-by-moderator interactions [39–42]. The nested structure of the data was modelled using dummy indicators for each study [40, 43]. This was in contrast to the registered protocol but required because methods based on mixed-effects models showed significant problems with model convergence, making it unfeasible to use them for the imputation of missing data [44]. The imputations were carried out separately for each treatment group (intervention vs. control), thus taking both heterogeneity and possible treatment-by-moderator interactions into account. Both sporadically and systematically missing values were imputed [41, 42]. All variables at the study and participant level were considered as predictors of missing data. However, due to systematic missing data in some studies and multicollinearity between study-level predictors (e.g., between study ID and intervention format), we encountered estimation problems with the effects of some study-level predictors. In such a case, the procedure was adjusted such that it included the largest subset of predictors for which estimation was possible. Based on this procedure, we generated 100 imputed data sets, each after 50 iterations of the imputation algorithm. A detailed documentation of the procedure can be requested from the corresponding author.

Outcome Measures

The following types of outcome criteria were used: (a) DSS, (b) treatment response (evaluated in two different ways: (1) reliable change index [RCI] [18]; (2) 50% reduction in symptoms), (c) close to symptom-free status (e.g., scoring below a predefined cut-off score, i.e. 13.00 for BDI-II [45, 46] and 11.88 for CES-D [47]), (d) symptom deterioration (defined by (1) RCI; (2) 50% increase in symptoms) and (e) time to MDD onset (e.g., DSM-IV criteria assessed with the telephone-administered SCID or the web version of the WHO Composite International Diagnostic Interview, CIDI). Standardized depression outcome measures (BDI-II [48]; CES-D [49]) were transformed into standardized t value scores (i.e., population mean of 50 and standard deviation of 10), using the common metric approach [50]. After the imputation procedure the common metric was backtransformed into the original metric and then transformed into treatment response, close to symptom-free status and deterioration rates.

Moderators of Intervention Effects on DSS

The following sociodemographic characteristics were included: sex [51–54], age [51, 55], relationship status [51, 56], education [57, 58] and employment [56]. Initial DSS [59–62], initial anxiety symptoms [63] measured with the HADS-A questionnaire or via CIDI interview, comorbid mental health problems [55] measured with distress scales (K6, PAID) or the Web Screening Questionnaire, previous psychotherapy for depression, use of antidepressants [58] and chronic medical conditions [51, 55, 59] were examined in terms of clinical characteristics. The format of the Internet intervention (e.g., guided, unguided) as well as the length of the treatment [64] were analysed as intervention characteristics on study level.

IPD Meta-Analysis

For the IPD-MA we utilized a one-step data analysis approach because the effects of moderators and study level covariates can be examined more precisely, compared to the two-step procedure

Table 1. Selected characteristics of eligible randomized controlled trials examining the effects of psychological treatments of subthreshold depression in adults

Author	Target group	Definition of subthreshold depression	Conditions	*N*	Format	Sessions	Follow-up		Quality criteria[a]	Country
							1	2		
Buntrock [20, 21], 2015	Adults (19–78 years)	CES-D ≥16, SCID: no MDD	1. iCBT 2. OPE + TAU	202 204	Guided	6	+	+	+ + + +	Germany
Ebert [96], 2018	Adults (21–75 years)	CES-D ≥16, SCID: no MDD	1. iCBT 2. WL	102 102	Guided	6	+	–	+ + + +	Germany
Imamura [25, 74], 2014	Employees (21–62 years)	CIDI: no MDD	1. iCBT 2. TAU	231 223	Unguided	6	+	–	+ + s +	Japan
Klein [73], 2016	Adults (18–65 years)	PHQ ≥5 ≤14; MINI: no MDD	1. iCBT 2. TAU	355 368	Guided/ unguided	12	+	+	+ + + +	Germany
Nobis [71], 2015	Diabetic patients (19–80 years)	CES-D ≥23, SCID: no MDD	1. iCBT 2. OPE + TAU	55 61	Guided	6	+	–	+ ± s +	Germany
Spek [75], 2007	Older adults (44–72 years)	EDS >12, no MDD; CIDI: no MDD	1. iCBT 2. WL	102 100	Unguided	10	–	+	+ + s +	The Netherlands
Van Bastelaar [72], 2011	Diabetic patients (19–82 years)	CES-D ≥16; CIDI: no MDD	1. iCBT 2. WL	40 41	Guided	8	+	–	+ + + +	The Netherlands

CES-D, Center for Epidemiological Studies Depression Scale; SCID, Semi-Structured Clinical Interview for DSM-4 or -5; CIDI, Composite International Diagnostic Interview; PHQ, Patient Health Questionnaire; MINI, Mini International Neuropsychiatric Interview; EDS, Edinburgh Depression Scale; MDD, major depressive disorder; iCBT, internet-based cognitive-behavioural therapy; OPE, online psychoeducation; TAU, treatment as usual; WL, waiting list. [a] In this column a positive (+), negative (–) or unclear (±) sign is given for four quality criteria, respectively: allocation sequence; concealment of allocation to conditions; blinding of assessors; intention-to-treat analyses; all studies were rated as fulfilling the "intention-to-treat" criteria, as multiple imputation was used for all studies to handle missing data. An "s" indicates that only self-report instruments were used as outcome measure.

[65]. In the protocol [32], we defined that we additionally planned to conduct a two-step meta-analysis on study level to examine whether studies that did not provide data might bias the results of our IPD-MA. However, this was not necessary, as we were able to include the primary data of all identified trials on Internet-based interventions to treat sD in the current study. All analyses except for the survival analyses were carried out with the imputed data set. Due to the relatively high missing rates of FU1 and FU2, additional sensitivity analyses were performed and reported with the original data for our primary outcome (DSS).

Effects on DSS

We used a multilevel regression analysis predicting DSS scores from treatment group while controlling for baseline DSS. We included both a random intercept and random slope for the treatment effects to capture both unobserved heterogeneity between study populations (intercept) and study efficacy (slope). Models were fitted to all multiply imputed data sets, and final parameter estimates were aggregated via Rubin's rule [66], using the *lme4* [67] and mitml [68] packages in R version 3.5.2. Hedges' g and corresponding 95% CI were calculated as a standardized effect size measure, using the populations' standard deviation (SD = 10) of the common metrics.

Effects on Response, Close to Symptom-Free Status and Deterioration

We used multilevel logistic regression analyses including both a random intercept and random slope for the treatment effects. We proceeded to calculate odds ratios (OR) and 95% CI to further investigate differences between intervention groups. In addition, we calculated the numbers needed to benefit (NNTB) or the numbers needed to harm (NNTH) in order to achieve one additional response, respectively, close to symptom-free status or case of deterioration as compared to the control group [69].

Effects on Depression Onset

Time to MDD onset was expressed in weeks. The mean survival time was calculated as the area under the Kaplan-Meier survivor function within the 12-month study period. Differences in survivor functions between intervention groups were analysed using the log rank test. The nested structure of the data was not taken into consideration for these two analyses. In addition, we used Cox proportional hazard regression models (based on mixed-effects models to handle the nested data structure) controlling for initial DSS to investigate differences in time to onset of MDD between intervention and control groups. The proportional hazards assumption was evaluated using the scaled Schoenfeld residual test [70].

Moderators of Intervention Effects on DSS

We explored moderators of the intervention effect by including selected participant level and study level variables as well as their interaction with the intervention in the multilevel regression analyses. To reduce the complexity for moderator analyses we focused on DSS at posttreatment assessment only.

Table 2. Means, standard deviations and percentage of outcome variables at baseline, posttreatment time point (post), follow-up 1 and follow-up 2

	Intervention (n = 1,088)				Control (n = 1,098)				All (n = 2,186)			
	n	%	mean	SD	*n*	%	mean	SD	*n*	%	mean	SD
Depressive symptom severity												
Baseline			63.44	5.24			63.58	5.34			63.51	5.29
Post			57.23	8.45			60.80	8.09			59.02	8.46
FU1			57.10	8.92			59.74	8.49			58.42	8.80
FU2			60.47	10.32			62.55	10.23			61.51	10.33
RCI improvement												
Post	437	40.2			241	21.9			678	31.0		
FU1	430	39.5			307	28.0			737	33.7		
FU2	360	33.1			272	24.8			632	28.9		
50% decrease in symptoms												
Post	317	29.1			146	13.3			463	21.2		
FU1	326	30.0			199	18.1			525	24.0		
FU2	272	25.0			195	17.8			467	21.4		
Close to symptom-free status												
Post	379	34.8			232	21.1			611	28.0		
FU1	412	37.9			280	25.5			692	31.7		
FU2	344	31.6			264	24.0			609	27.9		
RCI no change												
Post	598	55.0			776	70.7			1,374	62.9		
FU1	586	53.9			707	64.4			1,293	59.1		
FU2	502	46.1			549	50.0			1,051	48.1		
RCI deterioration												
Post	54	5.0			81	7.4			135	6.2		
FU1	72	6.6			84	7.7			156	7.1		
FU2	226	20.8			277	25.2			503	23.0		
50% increase in symptoms												
Post	52	4.8			63	5.7			115	5.3		
FU1	57	5.2			66	6.0			123	5.6		
FU2	187	17.2			217	19.8			404	18.5		

Percentages and absolute numbers are estimated based on multiple imputation. *N*, number of participants; SD, standard deviation; FU, follow-up; RCI, reliable change index.

Results

Study Selection and IPD Obtained

The flow chart inclusion of studies (online supplement 3) shows the selection process for included studies. The systematic search on psychological treatments for subthreshold depression resulted in a total of 16,407 abstracts (12,196 after the removal of duplicates), of which 1,885 full-text articles of RCTs on treatments for depression were retrieved. Of the 27 identified studies investigating the efficacy of psychological treatments for sD, we were able to obtain raw data from 21 data sets. While preparing the pooled data set, 5 further studies were published and could be integrated, resulting in a final sample of 26 primary study data sets. Of those 26 studies, 7 evaluated an Internet-based intervention and were thus included in the current IPD-MA.

Study Characteristics

Primary data had been successfully obtained from all of the 7 identified studies. An overview of study characteristics can be found in Table 1. Three of these studies included participants diagnosed with MDD [71–73], and one study additionally included participants with no ele-

Table 3. Multilevel regression analyses predicting depressive symptom severity scores from treatment group

DSS	Posttreatment time point			Follow-up 1			Follow-up 2		
	est.	SE	*p*	est.	SE	*p*	est.	SE	*p*
Fixed effects									
Intercept (b_0)	17.268	2.352	<0.001	14.945	2.618	<0.001	24.743	3.544	<0.001
Condition (b_1)	–3.874	0.705	<0.001	–3.028	0.767	<0.001	–2.688	1.037	0.01
Baseline DSS (b_2)	0.685	0.035	<0.001	0.705	0.039	<0.001	0.558	0.047	<0.001
Random effects (var)									
Intercept (τ^2_0)	2.559			3.247			24.61		
Condition (τ^2_1)	2.249			2.437			3.384		
Covariance intercept-condition ($\tau 2^0_1$)	–1.101			–1.231			4.136		

The multilevel regression analyses were controlled for initial depressive symptom severity. b_0, Y-intercept; b_1, treatment condition; b_2, initial depressive symptom severity; τ^2_0, intercept variance; τ^2_1, slope variance; est., estimate; SE, standard error; p, probability.

vated depressive symptoms [74]. These participants were excluded on an individual basis using the primary data. As one RCT was a three-arm design [75] we only included the condition of interest (online treatment) compared to the control condition and neglected the third arm (face-to-face treatment). This process resulted in a data set with the primary data from 2,186 cases (1,088 in the intervention groups, IGs, and 1,098 in the control groups, CGs).

Risk of Bias Assessment

The quality assessment of the included studies based on the published reports can be found in Table 1. Overall risk of bias was low. All studies reported an adequate sequence generation and reported blinding of outcome assessors or used self-report outcomes. Six of 7 studies reported an allocation to conditions by an independent (third) party; in 1 study there was no information given. All studies followed an intention-to-treat principle. Six of 7 studies met all 4 quality criteria; the remaining study met 3 of 4 criteria. Agreement between raters on the risk of bias was high across studies with Cohen's $\kappa = 0.94$.

Demographics and Clinical Characteristics

Participant characteristics at baseline are shown in online supplement 4. More than half of the participants were female (58.6%), with an average age of 44 years (SD = 11.6), in a relationship (58.2%) and employed (78.6%). At baseline, 25.8% of the participants used antidepressants. Moreover, 45.2% of the individuals had already undergone psychotherapy at some point in their lives, 33.5% suffered from comorbidities, and 51.4% reported chronic medical conditions. The mean initial depressive symptom level (common metrics) was 63.51 (SD = 5.29), which equals a value of 1.3 SD above the population average. There were no clinically important differences between treatment conditions in terms of any baseline characteristics. The most common patterns of missing values can be found in online supplement 5. More than half of the participants (58.6%) did not provide data on chronic medical conditions. There was also a remarkable amount of missing data in terms of DSS at FU2 (58.0%; see also Table 1 for an overview which trials assessed data at FU1 and at FU2), previous psychotherapy (56.7%) and comorbid anxiety (49.5%).

Effects on DSS

Means, standard deviations and percentage of multiply imputed outcome variables at baseline, posttreatment, FU1 and FU2 are displayed in Table 2. Effects on short- and long-term symptom severity are displayed in Table 3. A statistically significant difference in DSS was found between the IG and the CG at posttreatment assessment (b = –3.874, 95% CI: –5.26, –2.49; $t(17{,}229) = -5.49$, $p < 0.001$; Hedges' g = 0.39 [95% CI: 0.25–0.53]), at FU1 (b = –3.028, 95% CI: –4.53, –1.52; $t(4{,}467) = -3.95$, $p < 0.001$; g = 0.30 [95% CI: 0.15–0.45]) and at FU2 (b = –2.688, 95% CI: –4.72, –0.66; $t(549) = -2.59$, $p = 0.010$; g = 0.27 [95% CI: 0.07–0.47]). Slope variance was relatively low at posttest time point compared to FU1 and FU2 (Table 3). This rise in slope variance may be interpreted as an increase in the heterogeneity of intervention effects over time. Therefore, we repeated the analyses for FU1 and FU2 with the studies that provided original data

Table 4. Results from separate multilevel regression analyses on the effects of putative moderators on differential change in depression severity from baseline to posttreatment assessment

Baseline variable	Interaction: baseline variable × treatment condition					
	estimate	SE	*t* value	*p* (<|t|)	τ^2_0	τ^2_1
Age	–0.066	0.033	–2.002	0.045	2.812	1.972
Gender	–0.799	0.784	–1.02	0.308	2.568	1.998
Relationship	–0.549	0.707	–0.776	0.438	2.506	2.281
Employment	0.105	0.903	0.116	0.908	2.612	2.256
Previous psychotherapy	0.816	0.960	0.849	0.396	2.671	2.365
Depression medication	0.594	0.090	0.600	0.548	2.671	2.312
Comorbidities	–0.816	0.846	–0.965	0.335	2.825	1.904
Chronic medical conditions	–0.306	1.392	–0.22	0.826	2.639	2.197
Comorbid anxiety	–0.950	0.905	–1.049	0.295	2.996	2.086
Initial symptom severity	–0.182	0.069	–2.641	0.008	2.197	1.391
Format	–1.797	0.944	–1.905	0.057	2.655	0.786
Number of sessions	–0.001	0.256	–0.007	0.994	2.580	2.443
Education	–0.566	0.605	–0.936	0.350	2.597	2.621

All analyses were controlled for initial depressive symptom severity. SE, standard error; τ^2_0, intercept variance; τ^2_1, slope variance; gender (0 = male, 1 = female, 2 = other); relationship (0 = single/divorced/separated/widowed, 1 = married/in a relationship); employment (0 = no, 1 = yes); previous psychotherapy (0 = no, 1 = yes); depression medication (0 = no, 1 = yes), comorbidities (0 = no, 1 = yes), chronic medical conditions (0 = no, 1 = yes), comorbid anxiety (0 = no, 1 = yes), format (0 = unguided, 1 = guided); education (0 = no = 0–5 years, 1 = low = 6–9 years, 2 = middle = 10–12 years, 3 = high = 13–17 years, 4 = very high = 18+ years).

for these measurement points (n = 1,329; 61% of the total sample; online supplement 6). The results remained essentially the same but the group difference at FU2 became scarcely not significant (p = 0.055).

Effects on Response, Close to Symptom-Free Status and Deterioration

Response

Rates of response, close to symptom-free status and deterioration are displayed in Table 2. Significantly more participants in the IG showed a reliable improvement, both based on the RCI and 50% reduction in DSS compared to controls (RCI: OR = 2.46; 95% CI: 1.99–3.04; p < 0.001; 50% reduction: OR = 2.72; 95% CI: 2.12–3.49; p < 0.001). Differences remained statistically significant at FU1 (RCI: OR = 1.73; 95% CI: 1.40–2.15; p < 0.001; 50% reduction: OR = 1.96; 95% CI: 1.54–2.49; p = 0.001), and at FU2 (RCI: OR = 1.66; 95% CI: 1.18–2.34; p = 0.004; 50% reduction: OR = 1.64; 95% CI: 1.11–2.41; p = 0.013). The NNTBs based on the RCI (50% symptom reduction) were 5.49 (95% CI: 4.54–6.94) [NNTB = 6.31 (95% CI: 5.21–8.02)] at posttreatment assessment, 8.65 (95% CI: 6.45–13.11) [NNTB = 8.45 (95% CI: 6.50–12.06)] at FU1 and 12.03 (95% CI: 8.26–22.08) [NNTB = 13.81 (95% CI: 9.38–26.21)] at FU2.

Close to Symptom-Free Status

At the posttreatment time point, at FU1 and at FU2 significantly more participants of the IG reached a close to symptom-free status, compared to controls (post: OR = 2.12; 95% CI: 1.69–2.65, p < 0.001; FU1: OR = 1.82; 95% CI: 1.46–2.26; p < 0.001; FU2: OR = 1.61; 95% CI: 1.09–2.38; p = 0.017). The NNTBs were 7.30 (95% CI: 5.74–10.02) at posttreatment assessment, 8.09 (95% CI: 6.16–11.77) at FU1 and 13.20 (95% CI: 8.83–26.12) at FU2.

Deterioration

At the posttreatment assessment, the risk of deterioration, both based on the RCI and 50% increase in DSS, was reduced in the IG compared to the CG but the difference was statistically significant only in the RCI at the post-measurement time point (OR = 0.65; 95% CI: 0.43–0.98; p = 0.038) and at FU2 (OR = 0.70; 95% CI: 0.50–0.99; p = 0.046), but not at FU1 (OR = 0.85; 95% CI: 0.58–1.25; p = 0.412). There was no statistically significant difference in 50% increase at any measurement point (post: OR = 0.82; 95% CI: 0.53–1.25; p = 0.345; FU1: OR = 0.84; 95% CI: 0.55–1.29; p = 0.419; FU2: OR = 0.82; 95% CI: 0.58–1.15; p = 0.242). In terms of RCI (50% increase) the online-based treatment was associated with 1 case of deterioration at the posttreatment assessment for every 41.43 (95%

CI: 22.58–250.08) [104.35 (95% CI: 33.35–10^6)] participants who received treatment. The NNTHs for FU1 and FU2 were 96.84 (95% CI: 31.35–10^6) [129.54 (95% CI: 36.99–10^6) and 22.44 (95% CI: 12.53–107.20) [38.82 (95% CI: 17.06–10^6)], respectively.

Effects on Depression Onset

Three of the 7 studies with $n = 1{,}583$ participants (72.4% of the whole sample) provided data on time to onset of MDD [20, 25, 73]. In total, 18.7% of the participants in the IG and 25.8% in the CG experienced the onset of MDD during the study period. Online supplement 7 shows the Kaplan-Meier survival curves for the IG and CG generated for the 12-month study period. The Kaplan-Meier estimates of the cumulative incidence of MDD were 26% (95% CI: 22–30%) for the IG and 34% (95% CI: 30–37%) for the CG. The log-rank test revealed a statistically significant difference between incidence rates over time ($p = 0.004$). The mean time to onset of MDD within the 12-month trial period was 33 weeks in the IG and 32 weeks in the CG. Cox regression, which controlled for initial DSS, revealed a hazard ratio of 0.72 (95% CI: 0.58–0.89), which means that the risk of developing an MDD within 12 months is reduced by 28% in the IG compared to the CG when controlled for initial DSS. The estimated hazard ratio for DSS at baseline was 1.09 (95% CI: 1.06–1.11). There was no evidence for non-constant hazard ratios (global test of non-proportionality, $p = 0.568$; treatment condition, $p = 0.501$; DSS, $p = 0.689$).

Moderators of Intervention Effects on DSS

Results of separate multilevel regression analyses, each examining interactions of moderator × intervention effects, are displayed in Table 4. Results indicated initial DSS ($p = 0.008$) as well as age ($p = 0.045$) to be significant moderators of short-term treatment effects, with high initial DSS and older age associated with greater intervention effects (online supplements 8, 9). Afterwards, this analysis was repeated with both identified moderators and their interaction effects in one model to determine whether they are independent of one another. Results remained the same (online suppl. supplement 10).

Neither any of the sociodemographic characteristics (sex, relationship status, employment, education) nor any other clinical characteristics (anxiety symptoms, comorbid mental health disorder, previous psychotherapy for depression, use of antidepressants, chronic medical conditions) or the length of treatment on study level were associated with differential treatment effects. Guided format hardly reached statistical significance ($p = 0.057$).

Discussion

Main Findings

We found that Internet-based interventions resulted in lower DSS, greater treatment response and close to symptom-free status at posttreatment assessment, FU1 and FU2, and a reduced risk of depression onset within 12 months compared with control conditions. A reliable symptom deterioration was found for the CG at the posttreatment time point and at FU2 but no significant differences between groups were found for symptom deterioration in terms of 50% symptom increase. Results of the moderator analyses indicated higher DSS and older age to be associated with statistically significantly greater short-term treatment effects. Guided interventions showed better effects compared to unguided interventions, but this effect barely reached statistical significance.

Comparison to Previous Research

The between-group effect sizes of g = 0.39, 0.30 and 0.27 found in our IPD-MA for reducing DSS at posttreatment assessment, FU1 and FU2, respectively, are somewhat higher than those reported in recent meta-analyses on the effects of preventive Internet-based interventions for the treatment of sD (d = 0.25 at posttreatment [15], d = 0.28 at posttreatment [16]; d = 0.35, 0.22, 0.14 at posttreatment, FU1 and FU2, respectively [17]). The greater effect sizes found in our IPD-MA could be explained by a higher symptom severity at baseline as we only included indicated prevention studies that permit a greater potential for improvement, while Zhou at al. [16] also included universal prevention studies. The meta-analysis by Deady et al. [15] further included a study that evaluated a transdiagnostic trait-focused Internet-based intervention aimed at reducing symptoms of common mental disorders in university students [76], which is not directly comparable to cognitive-behavioural approaches used in other prevention studies. Furthermore, Sander et al. [17] included different interventions targeting a variety of indications like eating disorders or posttraumatic stress disorders with depression being only a secondary outcome in some cases, and there were also universal prevention studies included.

Previous meta-analyses based on comparisons of means could provide only little information regarding response and close to symptom-free status on an individual level. However, a recent IPD-MA on Internet-based interventions in patients with MDD found the IG to obtain significantly higher response and remission rates compared to controls after treatment (5–12 weeks) [47]. Ac-

cordingly, we have been able to show short-term effects on the intervention group in the period of up to 3–6 months after treatment in this IPD-MA as well. The positive effect persists up to 12 months.

There were no significant differences between the groups in deterioration rates in terms of 50% symptom increase but the IG was superior with fewer cases of reliable deterioration at the posttreatment assessment and FU2 compared to the CG. We found the risk for deterioration to be decreased by 35% in the IG compared to the CG. The latter finding points in the same direction like the results from a recent IPD analysis on MDD, which found the risk for a reliable deterioration from baseline to posttreatment time point to be significantly lower in the intervention versus control condition (relative risk = 0.47, 95% CI: 0.29–0.75) [77].

We found a risk reduction of 28% to develop an MDD within a year. This is similar to the results in a meta-analysis on preventive interventions for depression including 17 studies for indicated prevention, which found a mean risk reduction of 26% [78].

With regard to moderators, initial symptom severity and age were identified as moderators on DSS at posttreatment assessment. Guided format just missed the significance level.

The higher the initial DSS, the lower the depressive symptomatology at posttreatment assessment in the IG compared to the CG. Previous research on depression prevention interventions showed inconsistent results with one trial that found low initial DSS leads to a better outcome [79], while two other trials found the opposite effect [80, 81] and several trials that did not find any moderating effect at all (e.g., [82, 83]). Evidence on the impact of initial DSS in the field of MDD is conflicting as well (e.g., [47, 84, 85]). Given limited health care resources, future studies should identify the level of depression with an ideal cost-benefit ratio. Furthermore, higher age was associated with greater intervention effects on DSS at posttreatment assessment as well. This was also found in a recent meta-analysis based on individual participant data (IPD-MA) on Internet-based treatment of MDD [47] but in the field of sD several single trials led to mixed results: Vázquez et al. [82] for example showed that younger nurses benefited more from the Internet-based cognitive-behavioural therapy (iCBT) programme than older ones while age was not shown to be a significant moderator for treatment success when comparing iCBT versus routine care in a study by Button et al. [61]. There was only a trend for guided format to be associated with greater effects compared to purely self-guided interventions. There are no other meta-analyses or reviews yet investigating guidance as a moderator in Internet interventions for sD, but another single trial did not find semi-standardized guidance in iCBT for mild to moderate depression to be more effective than fully standardized feedback on DSS but leading to higher attrition rates [86]. In the field of MDD, numerous meta-analyses of recent years showed a superiority of the interventions with guidance compared to no guidance [64, 87, 88]. No other moderators were identified. While Richards and Richardson [64] found the pooled effect size for studies evaluating Internet-based interventions for depression which used less than 8 sessions to be considerably higher than studies which used 8 or more sessions in participants with MDD, this could not be confirmed in our analysis for people with sD.

Clinical Implications and Recommendations for Future Research

Results from this IPD-MA have important implications:

First, so far there are no obvious reasons to exclude specific subgroups of individuals, as intervention outcome has been shown to be independent of gender, relationship status, employment status, comorbid mental health disorders, chronic medical conditions as well as previous depression treatment or use of antidepressants. Moreover, there seems to be a lower risk for deterioration and for depression onset when taking part in Internet-based interventions compared to treatment as usual. However, more research is needed to evaluate the potential of iCBT in specific subgroups (e.g., younger age groups, low initial symptom severity) to determine whether or not they benefit from this kind of interventions, not only related to the prevention of depression onset but also to other outcomes, such as quality of life. In particular, more research is necessary to assess the point at which depressive symptoms at the lower end of the severity spectrum become sufficiently persistent to warrant preventive interventions. It might be beneficial to tailor Internet-based interventions to the specific needs of these subgroups to achieve greater treatment effects. Since gender was not a significant moderator, more effort should be put into also reaching men who are experiencing depressive symptoms, who are usually underrepresented in preventive interventions, as they are likely to benefit equally to women. For example, recruitment strategies as well as male-specific adaptations to interventions might be needed to improve intervention uptake. Future studies should identify preferences for and

barriers to participation in preventive psychological interventions in general but especially among men [10]. Some evidence suggests that pre-intervention motivational interviewing might increase help-seeking among men [89].

Second, the role of guidance has not yet been sufficiently explored. While a guided digital intervention format seems to lead to an additional benefit for individuals with MDD, the availability of individualized feedback for people suffering from sD probably has less impact on the effectiveness of the Internet-based intervention. Furthermore, it has been argued that effect sizes for unguided Internet-based interventions found in RCTs might be overestimated for what can be expected in routine care, as the structure in clinical trials (e.g., clinical interviews and structured outcome assessment) might be an adherence-fostering element [90], which is assumed an important underlying mechanism of the treatment effect [91]. Moreover, individuals might be less motivated to participate in interventions in which no regular content feedback from a psychologist is offered, which would lead to a lower reach and thus lower overall effects in the target population. This assumption was supported by a web-based survey study on public attitudes toward guided Internet-based therapies [92]. However, the potential on a population level might still be high, as such interventions can be distributed to more participants within a given health care budget. A stepped care model could be kind of a compromise when affected individuals usually start using an unguided intervention in a first step and receive guidance in the case of non-response (second step).

Strengths and Limitations

A strength of this IPD-MA is the sufficient statistical power to provide information on the long-term effects of psychological Internet-based interventions, which had been largely unclear and inconsistent so far. In addition, conclusions regarding response, remission, symptom deterioration and depression onset could also be drawn from the study data. Using an IPD-MA approach allowed us to analyse moderating effects and to test whether the efficacy depends on individual participant criteria. This leads to crucial insights about best possible treatments for specific subgroups. Furthermore, the methodological quality of the included studies was very high so that we can assume that the results are robust.

However, the study also has some limitations. First, two thirds of participants were at least highly educated (>13 years of education). Hence, the generalizability of our results might be limited to participants with high educational levels. However, education was not a significant moderator of treatment effect. Thus, although low educated people are usually underrepresented in clinical trials, they might benefit from iCBT as well [47]. In addition, more research is needed to evaluate treatment effects in people with low socio-economic status and having low Internet affinity. Second, DSS was only assessed with self-report instruments. Depending on the symptom severity of an individual, clinician ratings or self-report might be more suitable. Therefore, it seems best to include both, clinician rating and self-report in clinical research [93]. Third, the estimate of the slope variance at FU2 is very large and so are the standard errors for the fixed effects in that model. This is likely an effect of the extreme rate of missing data for end points at FU2. Fourth, we were unable to consider further moderators in our analysis, because many relevant variables associated with differential treatment response or depression incidence in the literature, such as lifetime history of depression, childhood adversity, personal characteristics, quality of life or mastery, had not been included in many of the published studies, leading to high rates of missing data and cases in which study level characteristics were completely confounded with missingness. More studies are ultimately needed to provide insight into the effects of additional moderators. Special attention should be paid to a more specific investigation of the influence of pharmacotherapy in patients with subclinical depression and its interaction with Internet-based treatments [26]. Finally, because this is an emerging field there are still contradictory results in the literature on effect moderators. Therefore, even a meta-analysis with high statistical power and sophisticated and carefully performed statistical methods is unlikely to provide a concluding answer at this point of time [94, 95]. With a higher number of primary studies and therefore even higher statistical power, more knowledge about moderating effects might be gained in the nearby future.

Conclusions

The findings of this IPD-MA provide evidence for Internet-based interventions to be a suitable low-threshold intervention to treat individuals with subclinical depressive symptoms and a wide range of participant characteristics and, moreover, to reduce the incidence of MDD. Effects were especially pronounced for older participants when initial DSS was already substantial.

Statement of Ethics

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Disclosure Statement

D.D.E. and D.L. reported holding minor shares of the Institute for OnlineHealth Training (GET.ON), which aims to transfer scientific knowledge related to the present research into routine mental health care. This institute licenses some interventions under study [20, 21, 71, 96] from the Leuphana University, Lueneburg, to provide the intervention within routine preventive services of health insurance companies in Germany.

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Author Contributions

D.D.E. conceptualized and designed the study, P.C. contacted the primary authors, J.R. and C.B. were responsible for building the database with support from K.W. and M.D. J.Z. and M.H. were responsible for the data analyses, S.G. and J.Z. for the imputation procedure. J.R. drafted the manuscript, supervised by D.E. and C.B. All authors critically revised the paper, read and approved the final version.

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ONLINE-SUPPLEMENT

Supplement 1: Deviations from the protocol:

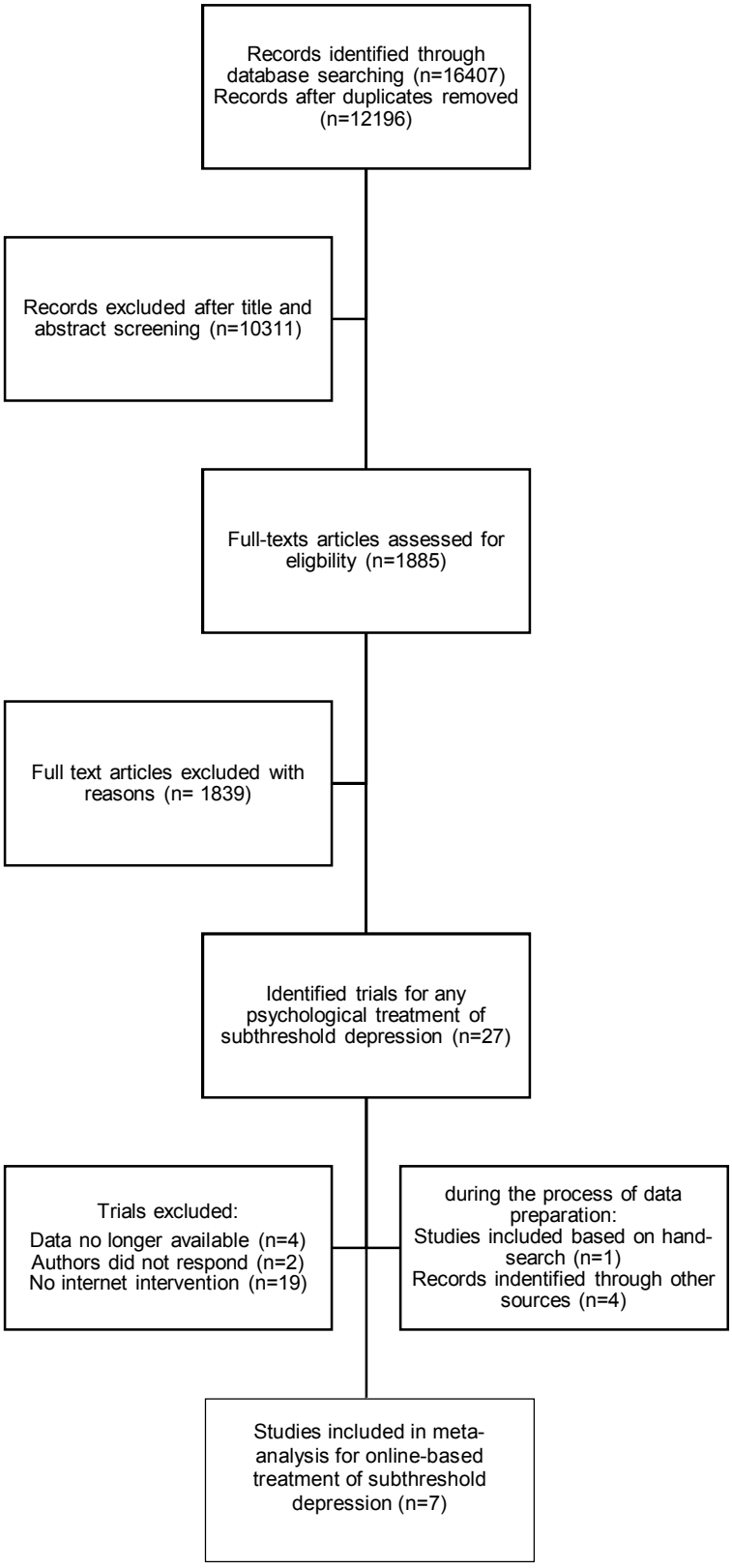
Details according to the protocol	Deviations from the protocol
The aim of the planned study was to examine the short-term and long-term as well as moderator effects of psychological interventions compared with control groups in adults with subthreshold depression.	In this IPD-MA we focus on internet-based psychological interventions only.
Next to outcomes like depressive symptom severity, treatment response, remission, symptom deterioration and MDD onsets it is planned to focus on quality of life, suicidal thoughts and behaviour, and anxiety as well.	We did not include quality of life, suicidal thoughts and behaviour, and anxiety into our analyses because most of the included trials did not provide data to these outcomes.
There was a long list of potential moderators in the protocol.	The planned list of moderators was much longer than those that have been eventually evaluated. When going through the relevant articles we noticed that several potential moderators have not been included in most of the trials. Therefore we had to shorten the list (see Supplement 2).

Supplement 2: Requested data to be included in the IPD dataset

Relevant authors were asked to provide the following data (if available):

Demographics	age, sex, ethnicity, country of birth, education, employment, marital status, income, children
Intervention details	randomised group, number of treatment sessions completed, number of weeks of treatment,
Clinical indicators	current diagnosis of depression, prior diagnosis of depression, number of previous depressive episodes, currently receiving antidepressants, previous psychotherapy, comorbid anxiety disorder, specific anxiety disorder, comorbid mental health disorder, comorbid physical health disorder, chronic medical condition
Outcome measures	diagnosed depression (baseline, post, follow ups), depressive symptom severity (baseline, post, follow ups), anxiety (baseline, post, follow ups), other symptom scales
Psycho-social measures	Quality of life, measures of interpersonal functioning
Other	measures of attitude, mastery

Supplement 3: Flowchart inclusion of studies



Supplement 4: Demographics and clinical characteristics

	Intervention (N = 1088)				Control (N = 1098)				All (N = 2186)			
	N	%	Mean	S.D.	N	%	Mean	S.D.	N	%	Mean	S.D.
Age, years			44.12	11.60			44.12	11.67			44.12	11.63
Gender, female	637	58.5			644	58.7			1281	58.6		
Currently in a relationship	646	59.4			628	57.2			1273	58.2		
Currently employed	866	79.6			852	77.6			1718	78.6		
Current use of antidepressants	276	25.4			287	26.1			563	25.8		
Previous psychotherapy	485	44.6			503	45.8			988	45.2		
Comorbidities	369	33.9			364	33.2			733	33.5		
Comorbid anxiety	428	39.3			452	41.1			880	40.3		
Chronic medical conditions	560	51.5			564	51.4			1124	51.4		
Education												
> none (0-5 years)	6	0.5			16	1.5			22	1.0		
> low (6-9 years)	74	6.8			70	6.4			144	6.6		
> middle (10-12 years)	291	26.7			272	24.8			563	25.8		
> high (13-17 years)	685	63.0			711	64.8			1396	63.9		
> very high (18+ years)	32	2.9			29	2.6			61	2.8		

Note: Percentages and absolute numbers are estimated based on multiple imputation.
Abbreviations: N = number of participants; S.D. = standard deviation

Supplement 5: Missing data patterns

N_p	format	num sess	age	sex	dss pre	empl	relat	educ	comorb	dss post	dep med	dss FU1	comorb anx	PPT	dss_FU2	CMC	N_a
320																	3
283																	1
203																	2
149																	2
118																	3
114																	5
84																	4
83																	1
74																	2
69																	5
60																	3
54																	4
40																	4
38																	6
34																	4
32																	7
28																	8
27																	7
23																	4
22																	5
17																	6
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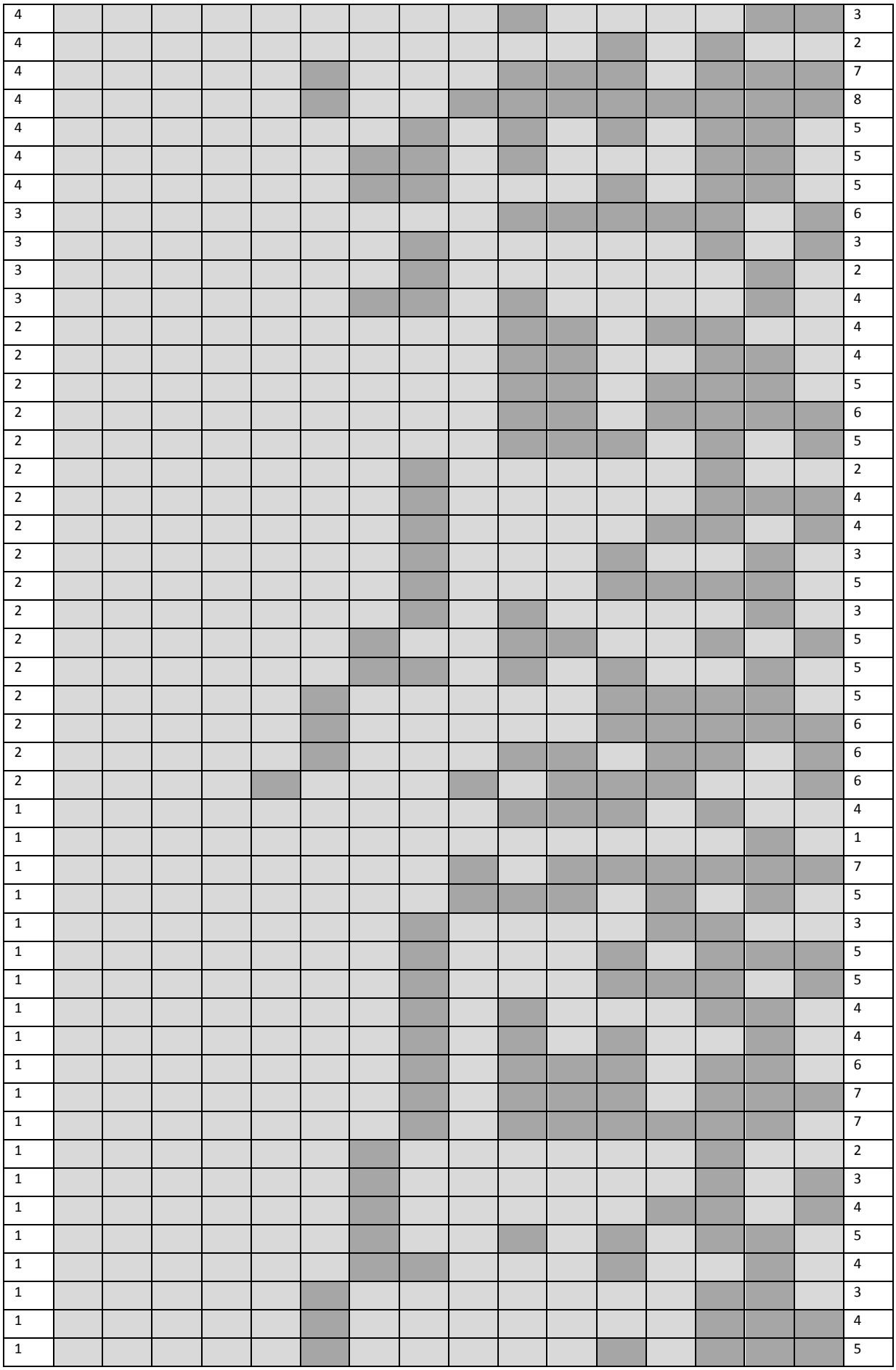

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	0	0	1	2	32	46	61	97	318	426	469	664	1083	1238	1268	1282	6987

Note: light grey = no missing data; dark grey = missing data; The left column (Np) tells the number of participants matching the pattern of the respective line; The bottom line (Nv) tells the number of missing data per variable; The right column (Na) tells the number of missing variables in that specific pattern;

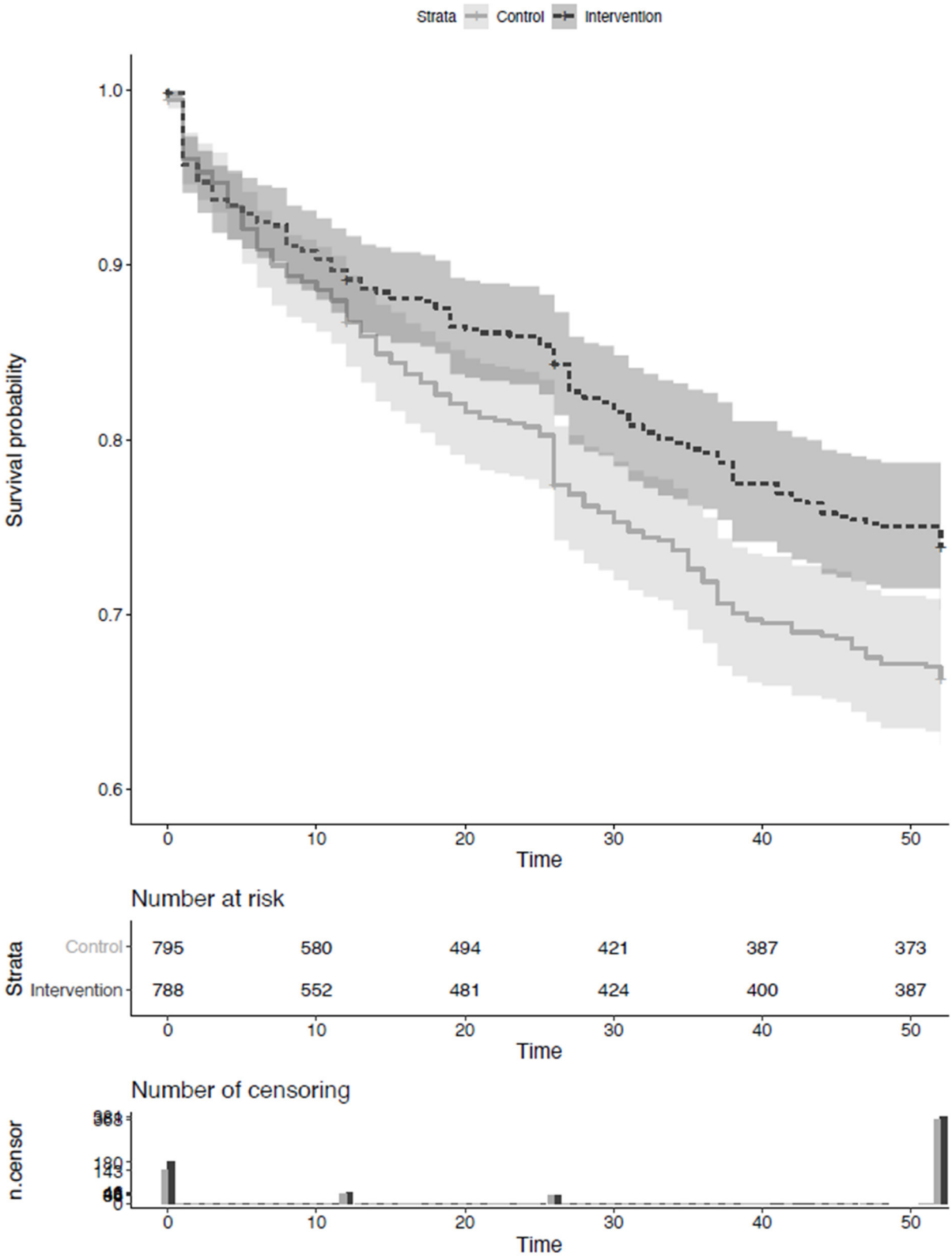
Abbreviations: num sess = number of sessions; dss pre = depressive symptom severity at pre-treatment; empl = employment; relat = relationship status; educ = education; comorb = comorbidities; dss post = depressive symptom severity at post-treatment; dep med= depression medication; dss FU1 = depressive symptom severity at follow-up-1; comorb anx = comorbid anxiety; PPT = previous psychotherapy; dss FU2 = depressive symptom severity at follow-up-2; CMC = chronic medical conditions;

Supplement 6: Multilevel regression analyses predicting depressive symptom severity scores from treatment group of studies that provided original data for FU1 (n = 1984) and FU2 (n = 1331)

	FU1			FU2		
	Est.	S.E.	p	Est.	S.E.	p
DSS						
Fixed Effects						
Intercept (b_0)	16.981	2.598	<0.001	27.845	5.693	<0.001
Condition (b_1)	-3.269	0.819	<0.001	-2.688	1.078	0.055
Baseline DSS (b_2)	0.681	0.039	<0.001	0.53	0.051	<0.001
Random effects (var.)						
Intercept (τ_0^2)	1.723			65.753		
Condition (τ_1^2)	2.599			2.606		
Covariance Intercept-Condition ($\tau 2_1^0$)	-0.728			12.573		

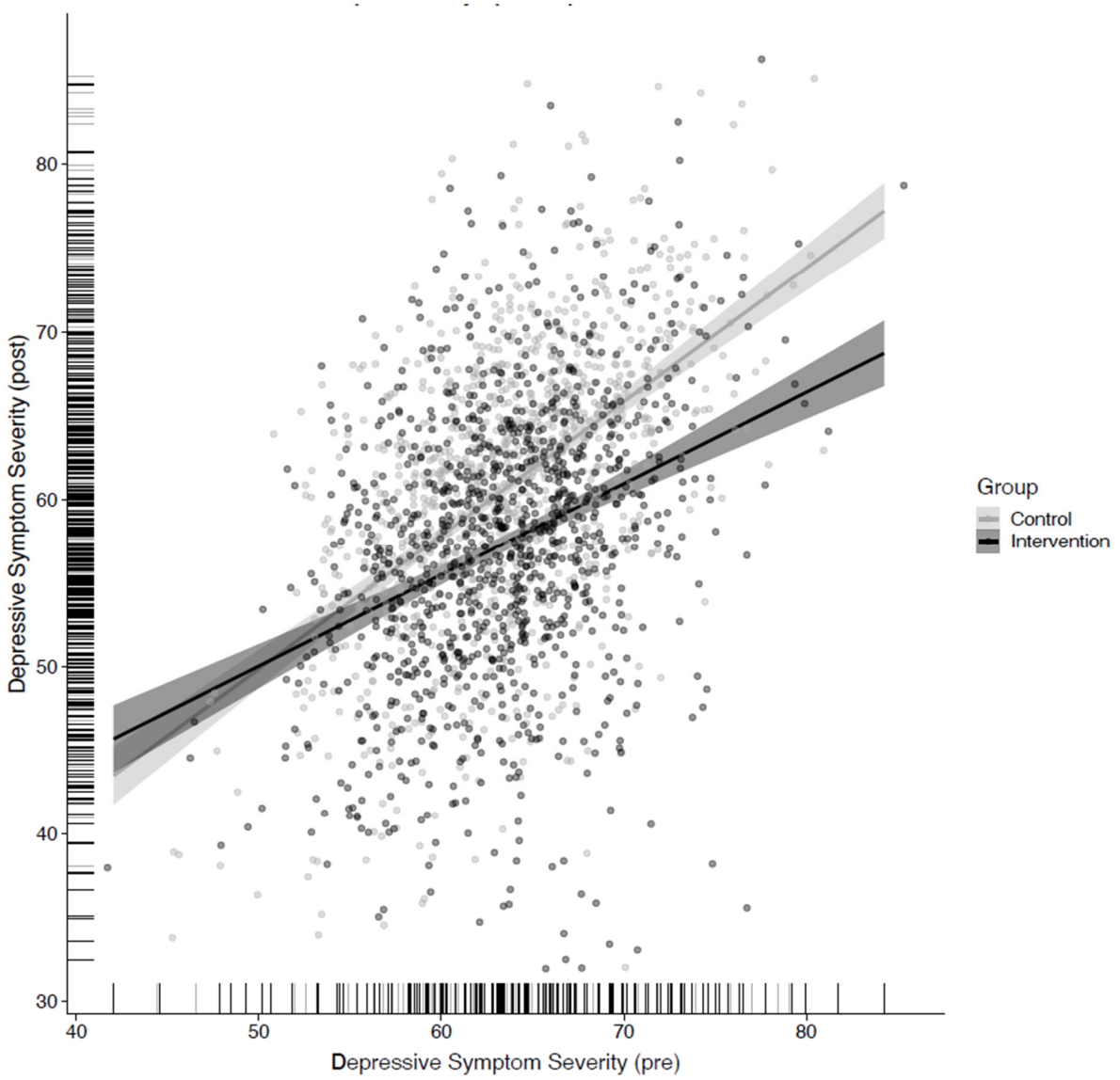
Note: The multilevel regression analyses were controlled for initial depressive symptom severity. b_0: Y-intercept; b_1: treatment condition; b_2: initial depressive symptom severity. τ_0^2: intercept variance; τ_1^2: slope variance;
Abbreviations: Est. = estimate; S.E. = standard error; p = probability

Supplement 7: Kaplan-Meier survival estimates of time to onset of major depressive disorder by study group



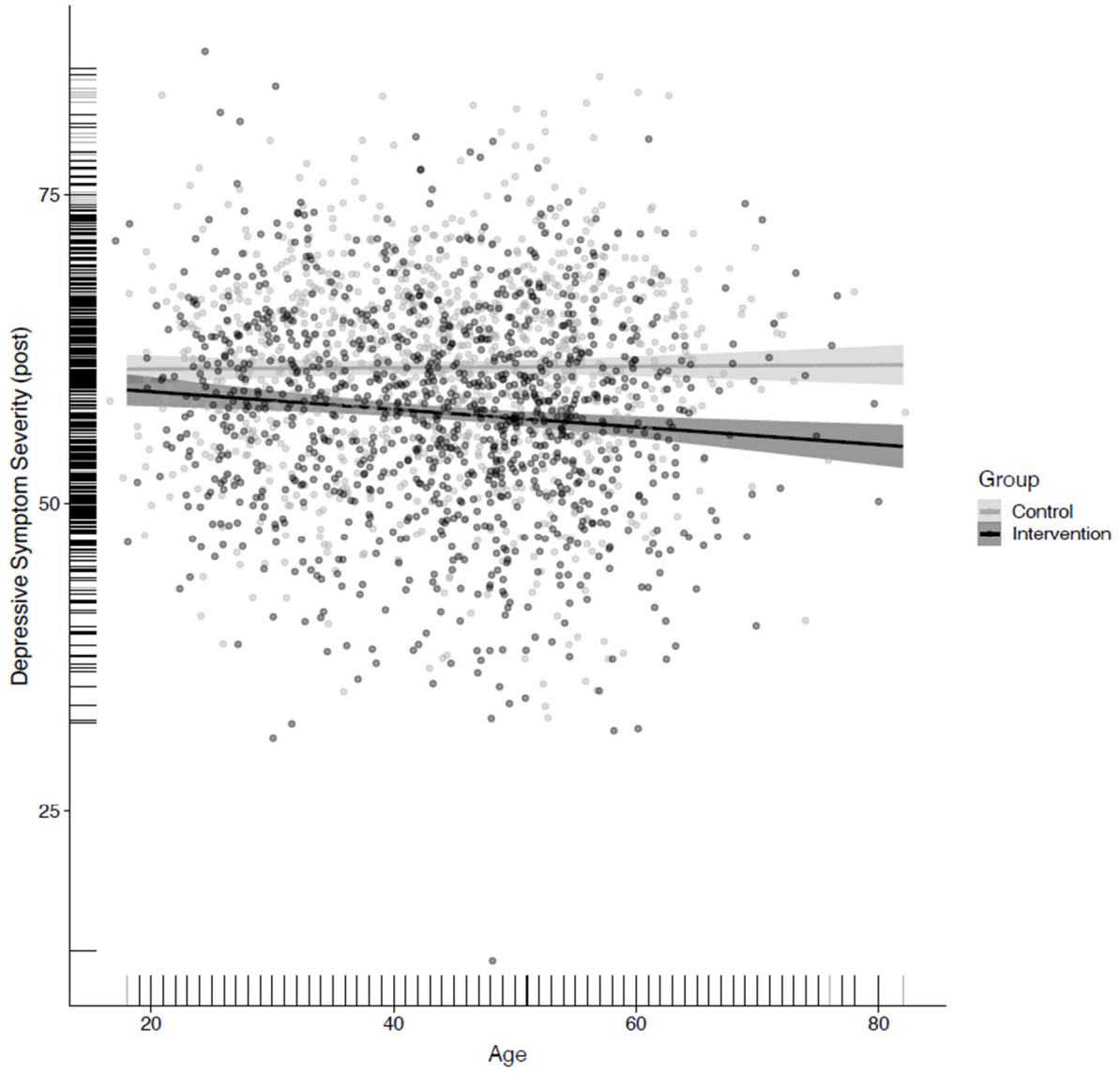
Note: The primary endpoint was time to onset (in weeks) of a major depressive disorder in the intervention relative to the control group according to DSM-IV criteria. Follow-up time was truncated at 52 weeks. The log-rank test and Cox proportional hazard regression analysis controlling for baseline depressive symptom severity were used to test for group differences. The shaded areas illustrate 95% CIs.

Supplement 8: Interaction effect of group and baseline symptom severity on depressive symptoms at post-treatment



Note: The light grey and dark grey dots represent the individual values of depressive symptom severity at post-treatment of participants in the control and intervention group, respectively. The shaded areas illustrate 95% CIs.

Supplement 9: Interaction effect of group and age on depressive symptoms at post-treatment



Note: The light grey and dark grey dots represent the individual values of depressive symptom severity at post-treatment of participants in the control and intervention group, respectively. The shaded areas illustrate 95% CIs.

Supplement 10: Results from multiple multilevel regression analyses on the effects of putative moderators on differential change in depression severity from baseline to post-treatment

Baseline variable	Main effect				Interaction: baseline variable x treatment condition			
	Estimate	Std. Error	t. value	p(<|t|)	Estimate	Std. Error	t. value	p(<|t|)
Group	11.188	4.661	2.400	0.016				
Age	0.222	0.222	0.985	0.325	-0.069	0.033	-2.110	0.035
Initial symptom severity	0.774	0.046	16.942	0.000	-0.185	0.069	-2.702	0.007

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REVIEW ARTICLE

Does Internet-based guided-self-help for depression cause harm? An individual participant data meta-analysis on deterioration rates and its moderators in randomized controlled trials

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Background. Almost nothing is known about the potential negative effects of Internet-based psychological treatments for depression. This study aims at investigating deterioration and its moderators within randomized trials on Internet-based guided self-help for adult depression, using an individual patient data meta-analyses (IPDMA) approach.

Method. Studies were identified through systematic searches (PubMed, PsycINFO, EMBASE, Cochrane Library). Deterioration in participants was defined as a significant symptom increase according to the reliable change index (i.e. 7.68 points in the CES-D; 7.63 points in the BDI). Two-step IPDMA procedures, with a random-effects model were used to pool data.

Results. A total of 18 studies (21 comparisons, 2079 participants) contributed data to the analysis. The risk for a reliable deterioration from baseline to post-treatment was significantly lower in the intervention *v.* control conditions (3.36 *v.* 7.60; relative risk 0.47, 95% confidence interval 0.29–0.75). Education moderated effects on deterioration, with patients with low education displaying a higher risk for deterioration than patients with higher education. Deterioration rates for patients with low education did not differ statistically significantly between intervention and control groups. The benefit–risk ratio for patients with low education indicated that 9.38 patients achieve a treatment response for each patient experiencing a symptom deterioration.

Conclusions. Internet-based guided self-help is associated with a mean reduced risk for a symptom deterioration compared to controls. Treatment and symptom progress of patients with low education should be closely monitored, as some patients might face an increased risk for symptom deterioration. Future studies should examine predictors of deterioration in patients with low education.

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Key words: Adverse events, depression, deterioration effect, Internet-based guided self-help, negative effects.

Introduction

Major depressive disorder (MDD) is not only highly prevalent (Alonso *et al.* 2004; Waraich *et al.* 2004; Kessler *et al.* 2005; Wittchen *et al.* 2011; Rozental *et al.* 2014) but also associated with substantial impairment

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(Ustün *et al.* 2004; Saarni *et al.* 2007) and economic costs (Berto *et al.* 2000; Greenberg & Birnbaum, 2005; Smit *et al.* 2006).

Psychological treatments have been shown to be effective in the treatment of depression (Cuijpers *et al.* 2008*a*, 2014). However, not all benefit from these treatments and many affected individuals remain untreated (Kohn *et al.* 2004; Wittchen *et al.* 2011).

Internet-based guided self-help interventions might be an acceptable (Cavanagh *et al.* 2011), effective (Johansson & Andersson, 2012; Richards & Richardson, 2012), and cost-effective (Hedman *et al.* 2012) treatment alternative, that could provide treatment to individuals not reached so far (Ebert *et al.* 2015*a*). While researchers have consistently demonstrated positive effects of Internet-based guided self-help for depression both, for adults (Richards & Richardson, 2012) and youths (Ebert *et al.* 2015*b*), little is known about potential negative effects of Internet-based psychological treatments for depression (Boettcher *et al.* 2014; Ebert *et al.* 2014*a*; Rozental *et al.* 2014). This is not unique for Internet treatments, as limited data are also available regarding negative effects for psychotherapy in general (Barlow, 2010; Emmelkamp *et al.* 2014).

While in pharmacological outcome research the standard is to always evaluate both risks and benefits of an intervention (Willan *et al.* 1997; Curtin & Schulz, 2011) psychotherapy outcome research has so far mostly focused on treatment benefits only (Lilienfeld, 2007; Dimidjian & Hollon, 2010).

Among different potential negative effects of psychotherapy one particularly unfavorable outcome is deterioration of symptoms as a consequence of treatment. Evidence from uncontrolled psychotherapy outcome studies indicates that a substantial number of patients experience a symptom deterioration while being in psychotherapy. The proportion of patients with symptom deterioration in these uncontrolled studies range from 3% to 14% (Smith & Glass, 1977; Mohr, 1995; Hansen *et al.* 2006; Lambert *et al.* 2006). This phenomenon of 'the deterioration effect' has been noted even in the early years of psychotherapy research (Bergin, 1966; Garfield *et al.* 1971).

With regard to Internet-based self-help treatments, it could be argued that such interventions may be associated with an even greater risk for symptom deterioration than face-to-face approaches. For example, for some individuals a self-help approach might not be intense enough (Kiluk *et al.* 2011). Further, individuals might be overstrained by trying to apply psychotherapeutic self-help strategies. Some therapeutic techniques could be inappropriately implemented by participants without direct guidance from a therapist. These problems could result in a further aggravation of hopelessness in severely affected individuals. It could also be argued that in face-to-face treatments it is much easier to observe and react to early signs of deterioration than it is via the Internet. Another potential negative effect could be that self-help treatments could lead to a delayed help-seeking, which could result in a further deterioration of symptoms, if the initial low-intensity self-help treatment should be not sufficient.

Despite the fact that the topic of potential negative effects of both Internet-based treatments (Kiluk *et al.* 2011; Boettcher *et al.* 2014; Rozental *et al.* 2014, 2015; Bengtsson *et al.* 2015) and face-to-face psychotherapy (Lilienfeld, 2007; Barlow, 2010; Dimidjian & Hollon, 2010; Linden, 2013; Ladwig *et al.* 2014) have recently gained attention in the literature, empirical evidence on potential negative effects drawn from randomized controlled trials (RCTs) is still almost absent (Lilienfeld, 2007).

RCTs are the most reasonable approach to determine whether a treatment is differentially associated with a deterioration in functioning or an increase in symptomatology (Dimidjian & Hollon, 2010). If a randomized trial shows that participants in the active condition show greater deterioration in functioning than those in the non-treatment control condition, one can confidently conclude that the deterioration was a consequence of therapy (Lilienfeld, 2007). However, given that the number of people deteriorating during treatment is expected to be small, randomized trials are mostly underpowered to examine this research question adequately.

Moreover, RCTs evaluating psychological treatments seldom report the number of patients who deteriorated during treatment, thus it is not possible to investigate mean deterioration effects found in randomized trials and its moderators using traditional meta-analytical approaches. Consequently, to the best of our knowledge, there is no meta-analytical review on symptom deterioration and its moderators within RCTs evaluating Internet-based treatments or psychological interventions for depression in general. Given the increasing popularity of Internet-based treatments in healthcare systems worldwide (Andersson *et al.* 2014), there is a pressing need to evaluate potential deterioration effects of Internet-based treatments.

Individual participant data meta-analysis (IPDMA) can overcome some of the limitations of conventional meta-analysis at the study level (Clarke, 2005; Riley *et al.* 2010). By collecting and pooling the primary data of individual trials, analyses can be conducted, which have not been reported in the original studies. Furthermore, trials designed to detect overall treatment effects have limited power to detect treatment × subgroup interactions (Brookes *et al.* 2004). By combining the primary data of multiple trials using an IPDMA approach, it is possible to obtain a large sample size with sufficient power to examine effects in relevant

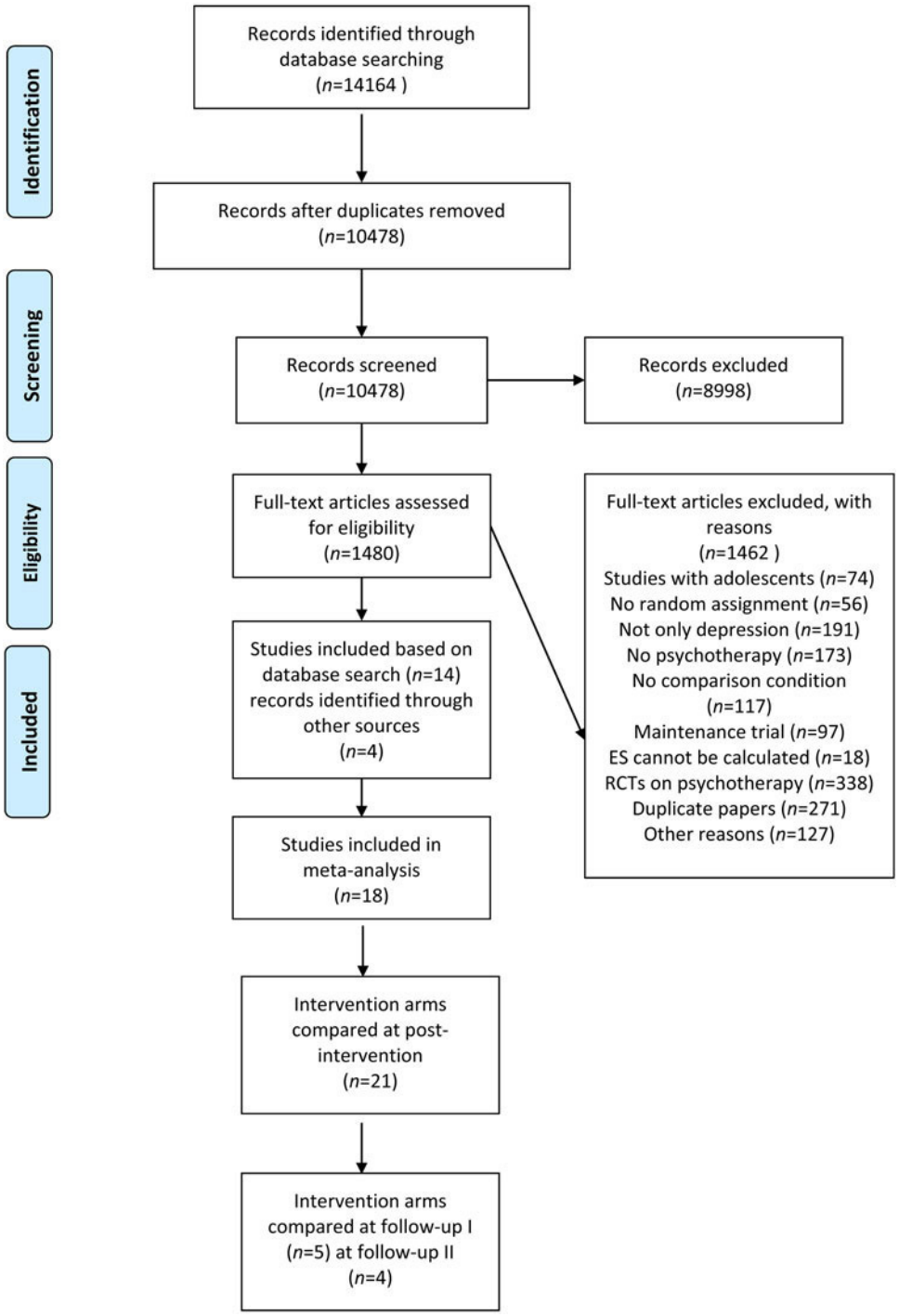

Fig. 1. Flowchart inclusion of studies.

subgroups and identify moderators of outcome (Cooper & Patall, 2009).

Hence, the present study aims to investigate deterioration rates and moderators of deterioration within randomized trials on Internet-based guided self-help interventions for adult depression, using IPDMA. We also evaluated deterioration rates in a number of subgroups of interest.

Method

Identification and selection of studies

In this study, we included randomized trials in which the effects of an Internet-based guided self-help treatment were compared with a control or comparison group (waiting list, care-as-usual, other) in adults (aged ⩾18 years) with depression (established by

diagnostic interview or elevated levels of depressive symptoms based on self-report measures). Studies were excluded if study participants were not currently in a depressive episode (e.g. if they were in remission), if the interventions were provided without guidance (i.e. without support from a therapist or other healthcare professional) in order to increase internal validity and to reduce potential heterogeneity, if the interventions were delivered to the individual via a group format or were delivered at a location that required the individual to travel to use the programme (e.g. a clinic). Co-morbid general medical or psychiatric disorders were not used as a study exclusion criterion. No language restrictions were applied. Fig. 1 shows the selection process for included studies.

For the identification of potential studies for inclusion, we used a database of 1476 papers on the psychological treatment of depression that has been described in detail elsewhere (Cuijpers *et al.* 2008*b*). These searches covered papers published until January 2014 and in these searches we examined 14 164 abstracts in Pubmed (3638 abstracts), PsycInfo (2824), EMBASE (4682), and the Cochrane Central Register of Controlled Trials (3020). These abstracts were identified by combining terms indicative of psychological treatment and depression (both MeSH terms and text words). Further, the primary studies from 42 meta-analyses of psychological treatment for depression were checked to ensure that no published studies were missed. From the 14 164 abstracts (10 474 after removal of duplicates) 1476 full-text papers were retrieved for possible inclusion in the database.

Data collection, characteristics of included studies and participants

Corresponding authors were contacted for each of the identified papers and asked to provide raw data from their study. Of the 15 published studies identified from the database search, primary data was obtained from 14 (Andersson *et al.* 2005; van Straten *et al.* 2008; Warmerdam *et al.* 2008; Perini *et al.* 2009; Ruwaard *et al.* 2009; Vernmark *et al.* 2010; Titov *et al.* 2010; Berger *et al.* 2011; van Bastelaar *et al.* 2011; Choi *et al.* 2012; Johansson *et al.* 2012*a*, *b*; Sheeber *et al.* 2012; Ünlü Ince *et al.* 2013). Data for one study (Titov *et al.* 2011) could not be obtained, as the dataset was no longer available to the Titov research team. The study that was not included did not differ from the other studies in terms of design, participants, intervention, or quality. We also asked all authors whether they were aware of other recently completed RCTs that met our inclusion criteria, but were not yet published. Four more studies were identified by this method, and the authors were all willing to contribute their primary data to this project (Carlbring *et al.* 2013; Newby *et al.* 2013; Ebert *et al.* 2014*c*; Kleiboer *et al.* 2015). This process resulted in a dataset with the primary data from 18 RCTs including 2079 cases. These 18 randomized controlled studies included 21 comparisons between an Internet-based guided self-help group *v.* control condition from baseline to post-test, five comparisons in addition from baseline to follow-up I (1–4 months, mean = 2.44, S.D. = 1.09, range 1–4, $n = 737$ participants) and four comparisons from baseline to follow-up 2 ($\geqslant$6 months, mean = 6.96, S.D. = 1.7, range 6–10, $n = 594$ participants). If a study had three conditions there would be two comparisons (i.e. the active treatment condition with each of the two control conditions). Only one study provided data for both follow-up time points (Ebert *et al.* 2014*b*). Characteristics of each included study are described in Table 1. Detailed information on sociodemographic and clinical characteristics of study participants can be found in Table 2.

Risk of bias assessment

The validity of included studies was assessed using four criteria of the 'Risk of Bias' assessment tool, developed by the Cochrane Collaboration (Higgins *et al.* 2011). This tool assesses possible sources of bias in randomized trials, including the adequate generation of allocation sequence; the concealment of allocation to conditions; the prevention of knowledge of the allocated intervention (masking of assessors); and dealing with incomplete outcome data (this was assessed as positive when intention-to-treat (ITT) analyses were conducted, meaning that all randomized participants were included in the analyses). Assessment of the quality was conducted independently by two assessors. Overall risk of bias was low. All studies reported an adequate sequence generation, and allocation to conditions by an independent (third) party. Sixteen studies reported blinding of outcome assessors or used only self-report outcomes, whereas five did not report blinding. All studies were coded as having handled missing data adequately, as ITT analyses were applied and missing data were imputed for all studies using multiple imputation. Sixteen studies met all four quality criteria, the remaining five studies met three of four criteria. Agreement between independent raters (P.C., L.D.) on the risk of bias was 95% across studies.

Missing data

Analyses were conducted according to the ITT principle. Missing data in the raw datasets were handled using multiple imputations (Schafer & Graham, 2002) with a Markov Chain Monte Carlo multivariate imputation algorithm (Missing data module in SPSS v. 20;

Table 1. *Selected characteristics of randomized controlled studies examining the effects of Internet-based psychotherapies for depression in adults*

Study	Recr	Depression	Inter-vention	N_{mod}	Time (weeks)	Guidance	*N*	Control group	*N*	Primary outcome	Duration of follow-up	Qual[a]	Publ	Country
1. Andersson *et al.* (2005)	Comm	MDD on CIDI-SF + MADRS-S 15–30	CBT	5	8	Feedback at the end of each module	62	Web-based discussion group	62	BDI-II	6 months	++++	1	SWE
2. Berger *et al.* (2011)	Comm	MDD on MINI + BDI-II >13	CBT	11	12	Weekly support via email by therapist	25	WL	26	BDI-II	6 months	++++	1	SWZ/ GER
3. Carlbring *et al.* (2013)	Comm	MDD on MINI-DIS + PS BDI-II >13	ACT	7	13	Weekly contact by psychologist	40	WL	40	BDI-II	–	++++	0	SWE
4. Choi *et al.* (2012)	Comm	MDD on SCID-I PHQ-9 score >18	CBT	6	8	Weekly support via email or telephone by therapist	25	WL	30	BDI	N.A.	++–+	1	AU
5. Ebert (2014*b*)	Comm	CES-D > 16	PST	5	5	Feedback at the end of each module	75	WL	75	CES-D	3 and 6 months	++++	0	GER
6. Johansson & Andersson (2012*a*)	Comm/ Clin	MADRS-S 15–35 MDD confirmed by telephone interview	PD	9	10	Contact via online platform by therapist	46	Brief scheduled therapist support	46	BDI-II	10 months	++–+	1	SWE
7. Johansson & Andersson (2012*b*)[a]	Comm/ Clin	MADRS-S >14 MDD on SCID-I	CBT*	8–10	10	Contact via email by therapist	37	Moderated web-based discussion group	42	BDI-II	N/A	++++	1	SWE
							36							
8. Kleiboer (2015)	Comm	CES-D score of 16–39 HADS score of 8–14	PST	5	5	Contact via email by coach	106	WL	106	CES-D	N.A.	++++	0	NL
9. Newby *et al.* (2013)	Comm/ Clin	MDD on MINI	CBT	6	10	Regular contact up to session 2, and response to user requests or decline in K10/ PHQ-9 scores	25	WL	37	BDI-II	N.A.	++–+	1	AU
10. Perini *et al.* (2009)	Comm	PHQ-9 score >4	CBT	6	6	Contact via email by therapist	27	WL	18	BDI-II	N.A.	++++	1	AU
11. Ruwaard *et al.* (2009)	Comm	BDI-IA score 10–29	CBT	8	11	Feedback on activities by therapist	36	WL	18	BDI-IA	N.A.	++++	1	NL
12. Sheeber *et al.* (2012)	Clin	Elevated self-reported levels of depression	CBT	8	8	Weekly contact via telephone	35	WL	35	BDI-II	N.A.	++++	1	USA
13. Titov *et al.* (2010)[a]	Comm	MDD on MINI	CBT	8	8	Weekly contact by therapist	38	WL	36	BDI-II	N.A.	++++	1	AU
			CBT	8	8		45							
14. Ünlü Ince (2013)	Comm	MDD on MINI CES-D >15	PST	5	5	Feedback on homework activities by coach	49	WL	47	CES-D	4 months	++++	0	NL

Table 1 (*cont.*)

Study	Recr	Depression	Inter-vention	N_{mod}	Time (weeks)	Guidance	*N*	Control group	*N*	Primary outcome	Duration of follow-up	Qual[a]	Publ	Country
15. Van Bastelaar *et al.* (2011)	Comm	MDD on CIDI CES-D >15	CBT	8	8	Feedback on homework activities by coach	125	WL	130	CES-D	1 month	++−+	1	NL
16. Van Straten *et al.* (2008)	Comm	Self-defined depression or anxiety	PST	4	4	Feedback by coach	107	WL	106	CES-D	N.A.	++++	1	NL
17. Vernmark *et al.* (2010)	Comm	MDD on SCID-I-CV	CBT	7	7	Support via email by therapist	29	WL	29	BDI	N/A	++−+	1	SW
18. Warmerdam *et al.* (2008)[a]	Comm	CES-D*	CBT	8	8	Weekly feedback by therapist	88	WL	87	CES-D	3 months	++++	1	NL
			PST	5	8		88							

Recr, Recruitment population; Comm, Community sample; Clin, Clinical Sample; Depression, confirmation of depression; CBT, cognitive behaviour therapy; ACT, acceptance and commitment therapy; PD, psychodynamic therapy; PST, problem-solving therapy; N_{mod}, Number of modules in the intervention; WL, waiting list control; BDI, Beck Depression Inventory; CES-D, Centre for Epidemiology Studies Depression Scale; Qual, risk of bias Score; Publ, publication of result (0 = unpublished, 1 = published); SWE, Sweden; SWZ, Switzerland; GER, Germany; NL, The Netherlands; AU, Australia; USA, United States of America.

[a] In this column a positive or negative sign is given for four quality criteria, respectively: allocation sequence; concealment of allocation to conditions; blinding of assessors; and intention-to-treat analyses.

Table 2. *Demographic and clinical characteristics*

	Intervention ($N = 1123$)			Control ($N = 956$)			All ($N = 2079$)		
	%	Mean	S.D.	%	Mean	S.D.	%	Mean	S.D.
Age, years		47.1	8.2		46.4	9.2		47.8	7.3
Female (%)	789 (70.57)			640 (66.04)			1419 (68.48)		
Married/partnership (%)	442 (49.44)			378 (47.61)			820 (48.58)		
Further education after high school (%)[a]	548 (59.05)			404 (54.16)			952 (56.87)		
BDI[b]									
Baseline		25.19	8.26		24.57	8.14		24.91	8.21
Post		13.24	8.98		21.01	10.09		16.78	10.26
Follow-up I[c]									
Follow-up II		12.23	8.25		14.52	8.81		13.39	8.6
CES-D[b]									
Baseline		28.86	8.4		28.46	8.42		28.67	8.41
Post		16.83	11.23		23.05	10.34		19.88	11.23
Follow-up I		17.80	8.75		22.72	8.34		20.05	8.91
Follow-up II		14.91	9.65		20.12	9.79		17.62	10.03
No current use of antidepressants[a]	27 (4.48)			11 (2.05)			38 (3.34)		
Comorbid anxiety disorder (%)[a]	308 (57.36)			288 (58.06)			596 (57.7)		

BDI, Beck Depression Inventory; CES-D, Centre for Epidemiological Studies Depression Scale.

[a] Percentages refer to those participants of studies who reported data.

[b] Medication: BDI and CES-D data refer to the imputed values.

[c] Studies that used the BDI as primary outcome did not assess follow-up I.

IBM Corp., USA) and 100 estimations per missing value. For the imputation of the primary outcome depression severity, we used all complete participant and study characteristics (study identifier, intervention group, baseline depression score, age, sex, recruitment population, confirmation of depression diagnosis method, intervention type, country of study, bias score – and post-intervention depression score when imputing follow-up). We did not impute baseline predictors.

Calculating deterioration rates

All studies used either the Centre for Epidemiological Studies – Depression Scale (CES-D; Radloff, 1977), or the Beck Depression Inventory (BDI; Beck *et al.* 1961) as outcome measures. Where multiple depression measures were present, the BDI was coded as the primary outcome measure given that it was the most frequently used outcome measure across studies. For both measures we calculated deterioration and response rates according to the widely used reliable change index (RCI; Jacobson & Truax, 1991). Participants whose scores from pre-treatment to post-treatment had RCIs below the cut point of −1.96 were considered to have experienced deterioration. A RCI of −1.96 is equivalent to increases of depression of 7.68 points on the CES-D; and 7.63 points on the BDI.

Analyses

Effects of Internet-based treatments on deterioration rates were calculated using the standard two-step IPDMA approach (Riley *et al.* 2010). Thus, after calculating whether or not a participant deteriorated (yes/no) we calculated event rates for each study separately on the basis of the imputed data. Following this, pooled event rates across studies were calculated according to a random-effects model as implemented in the Comprehensive Meta-analysis software package version 2.2.021 (https://www.meta-analysis.com), accounting for clustering of both participants' within-study and between-study heterogeneity (Abo-Zaid *et al.* 2013). We proceeded by calculating the relative risks for each study, and pooled the results across the studies using a random-effects DerSimonian–Laird model (DerSimonian & Laird, 1986). For all analyses we chose a random-effects model, as we expected considerable heterogeneity among the studies. If there were significant differences between the groups with regard to deterioration, response, and remission rates, we also calculated the number needed to harm (NNH) and/or the number needed to treat (NNT)

and the associated 95% confidence intervals (CIs), compared to the control group. The NNH indicates the number of participants treated in the experimental condition for one extra person to demonstrate symptom deterioration as compared to the control group. We also calculated a benefit–risk ratio (Willan *et al.* 1997), by dividing the NNH for one extra symptom deterioration through the NNT to achieve one response [response was also defined using the reliable change criteria, such that participants with a reliable positive change (+1.96 on the RCI) were considered responders]. This procedure is usually used within drug treatment research (Curtin & Schulz, 2011), and quantifies the numbers of favourable outcomes achieved for each additional unfavorable outcome event incurred. Benefit–risk ratios were only calculated if there is a higher risk of deterioration in the intervention group as compared to the control group (Willan *et al.* 1997).

Sensitivity analyses

To test the robustness of our findings, we also conducted a sensitivity analysis applying an alternative criterion for deterioration. We defined the alternative criterion for deterioration such that individuals whose depression scores at baseline increased by $\geqslant$50% at follow-up were categorized as having experienced deterioration. This criterion refers to a relative change instead of to an absolute change in symptoms.

Multiple treatments within one study

There were three studies in which two treatments were compared with a single control group (Warmerdam *et al.* 2008; Titov *et al.* 2010; Johansson *et al.* 2012*b*). In these cases, we treated each comparison as a separate study, and we avoided double counting of controls by randomly assigning half the control participants to each comparison.

Heterogeneity

As a test of homogeneity of effect sizes, we calculated the I^2 statistic as an indicator of heterogeneity in percentages (Ioannidis *et al.* 2007). A value of 0% indicates no observed heterogeneity, and larger values indicate increasing heterogeneity, with 25% as low, 50% as moderate, and 75% as high heterogeneity. We calculated 95% CIs around relative risks (RRs), using the non-central χ^2-based approach within the heterogi module for Stata (Orsini *et al.* 2013). We also calculated the Q statistic, but only report whether this was significant.

Publication bias

Publication bias was tested by inspecting the funnel plot and by Egger's test (Egger *et al.* 1997). We also applied Duval & Tweedie's trim-and-fill procedure (Duval & Tweedie, 2000), which yields an estimate of the effect size after the publication bias has been taken into account (Borenstein *et al.* 2009).

Subgroup analyses

We conducted a series of subgroup analyses. Pooling of the results was conducted according to the mixed-effects model. In this model, studies within subgroups are pooled with the random-effects model, while tests for significant differences between subgroups are conducted with the fixed-effects model. Subgroup analyses were only conducted for post-treatment data and not for follow-up data, as the sample sizes of follow-up datasets were not large enough to test for significant differences between subgroups. The following subgroups were investigated: *Participant characteristics*: sex (male/female); age group [adults (18–59 years), older adults ($\geqslant$60 years)]; education [low (up to high school), medium to high (high school degree or further education after high school)]; co-morbid anxiety disorder (yes/no); depression severity at baseline [mild to moderate (BDI < 29); severe (BDI $\geqslant$29)]; depression severity at baseline subgroup analyses was only calculated for participants of studies using the BDI, as the CES-D does not have an established cut-off score for depression severity. *Study characteristics*: MDD confirmed using an established diagnostic interview (yes/no); recruitment (community, clinical setting); risk of bias score [low (4); some risk (<4)]; type of control group (non-active/active). *Intervention characteristics*: theoretical model of the intervention (CBT, other); number of modules (4–5, 6–7, 8–11).

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Results

Deterioration rates

Overall pooled reliable deterioration rates across measurements are summarised in Table 3. The risk for a reliable deterioration from baseline to post-treatment was significantly lower in the intervention *v.* control conditions (RR 0.47, 95% CI 0.29–0.75) and the NNT

Table 3. *Deterioration rates in Internet-based treatments of depression, sensitivity, and subgroup analyses*

		N_{co}	ER_{IG} (95% CI)	ER_{CG} (95% CI)	RR (95% CI)	Z	I^2 (95% CI)	NNT/NNH (95% CI)[a]	p[b]
Deterioration rates	Post-treatment	21	3.36 (2.5–5)	7.6 (5.59–9.70)	0.47 (0.29–0.75)	−3.17**	0 (0–50)	43.21 (25.83 to 132.10)	
(RCI)	Follow-up I	5	2.80 (2.5–5)	6.10 (2.9–12.3)	0.47 (0.20–1.42)	−1.66†	0 (0–79)	71.43 (21.28 to −52.63)	
	Follow-up II	4	6.0 (3.3–10.7)	5.30 (2.8–9.8)	1.17 (0.49–2.87)	0.35	0 (0–90)	−142.86 (30.3 to −21.28)	
Alternative deterioration criteria (50% increase)	Post-treatment	21	3.12 (2.09–4.62)	5.20 (3.64–7.37)	0.51 (0.29–0.86)	−2.50**	0 (0–52)	76.92 (38.46 to 1000)	
	Follow-up I	5	2.35 (0.75–7.14)	4.36 (1.96–9.42)	0.70 (0.28–1.75)	−0.76	0 (0–85)	111.11 (35.71 to −90.91)	
	Follow-up II	4	3.92 (1.93–7.83)	4.37 (2.28–8.19)	0.83 (0.30–2.27)	−0.37	0 (0–90)	100 (22.22 to −38.46)	
Outcome measures separately	Only BDI	14	3.37 (2.02–5.56)	8.51 (6.03–11.87)	0.39 (0.20–0.76)	−2.75**	0 (0–58)	27.03 (15.63 to 100)	
	Only CES-D	7	3.09 (1.52–6.16)	5.57 (3.12–9.74)	0.56 (0.29–1.11)	−1.66†	6.92 (0–76)	55.56 (23.81 to 200)	
Study characteristics									
Diagnosis	Confirmed MDD	11	3.63 (2.09–6.23)	8.07 (5.50–11.70)	0.42 (0.21–0.85)	−2.40*	0 (0–60)	23.26 (25.64 to 333.33)	0.17
	Depressive symptoms	10	3.13 (1.80–5.40)	6.18 (3.76–9.98)	0.51 (0.27–0.97)	−2.06*	3.78 (0–72)	55.56 (13.51 to 83.33)	
Target group	General populations	18	3.53 (2.36–5.24)	7.89 (6.05–10.24)	0.42 (0.25–0.70)	−3.36***	0 (0–54)	33.33 (20.83 to 83.33)	0.87
	Specific populations	3	3.66 (1.75–7.49)	4.69 (1.10–17.84)	0.84 (0.21–3.35)	−0.25	34.33 (0–79)	166.67 (14.93 to −18.18)	
Recruitment	Community recruitment	16	3.81 (2.61–5.53)	6.64 (4.69–9.33)	0.53 (0.32–0.89)	−2.21*	0 (0–57)	52.63 (28.57 to 1000)	0.27
	Clinical samples	5	2.28 (0.86–5.92)	9.46 (5.67–15.37)	0.26 (0.09 to −0.82)	−2.49*	0 (0–79)	16.67 (9.35 to 76.92)	
Risk of bias score	Some risk (<4)	5	2.42 (1.09–5.27)	6.62 (3.33–12.72)	0.50 (0.18–1.39)	−1.32	0 (0–79)	27.78 (11.90 to −83.33)	0.89
	Low (4)	16	3.92 (2.64–5.77)	7.70 (5.71–10.32)	0.47 (0.28–0.78)	−2.88**	0 (0–57)	40 (23.26 to 166.67)	
Type of control	Active	4	3.50 (1.52–7.83)	5.45 (2.75–10.53)	0.60 (0.20–1.76)	−0.94	0 (0–85)	40(14.08 to −47.62)	0.21
	Non-active	17	3.57 (2.42–5.24)	7.52 (5.39–10.39)	0.45 (0.27–0.75)	−3.06**	0 (0–55)	38.46 (22.22 to 142.86)	
Intervention characteristics									
Intervention type	CBT	14	3.14 (1.96–5.00)	7.41 (5.07–10.71)	0.46 (0.25–0.87)	−2.39**	0 (0–58)	45.45 (22.73 to 2953.11)	0.91
	Other	7	3.35 (1.60–6.90)	7.05 (4.50–10.89)	0.49 (0.25–0.96)	−2.08*	0 (0–75)	37.04 (18.52 to −2821.37)	
No. of modules	4–5	8	4.23 (2.43–7.28)	7.33 (4.69–11.29)	0.58 (0.30–0·54)	−1.69	1.65 (0–71)	43.48 (19.23 to −166.67)	0.51
	6–7	3	1.61 (0.33–7.60)	7.59 (3.55–15.50)	0.18 (0.02–1.44)	−1.62	0[c]	22.73 (10 to −90.91)	
	8–11	10	2.85 (1.64–4.91)	6.90 (4.27–10.95)	0.41 (0.20–0.84)	−2.42*	0 (0–65)	45.45 (21.74 to −333.33)	
Patient characteristics									
Depression Severity	Mild-moderate	14	4.38 (2.53–7.48)	11.09 (7.43–16.23)	0.45 (0.23–0.94)	−2.12*	0 (0–60)	41.67 (17.24 to 90.91)	0.77
	Severe	14	5.37 (2.57–10.88)	9.20 (5.00–16.33)	0.36 (0.09–1.36)	−1.51	0 (0–79)	31.25 (11.11 to 38.46)	
Anxiety disorder	Yes	9	2.99 (1.50–5.87)	5.72 (3.47–9.28)	0.41 (0.16–1.01)	−1.87†	0 (0–54)	28.34 (15.31 to 190.53)	
	No	9	3.66 (1.70–7.69)	5.55 (2.84–10.56)	0.66 (0.22–1.97)	−0.75	0 (0–83)	238 (25.36 to −32.20)	0.52
Age group	Adults	21	3.51 (2.44–5.03)	7.97 (6.05–10.43)	0.46 (0.48–0.28)	−3.12**	0 (0–50)	45.45 (24.39 to 250)	0.84
	Old adults (⩾60)	19	7.56 (3.63–15.11)	10.67 (5.75–18.97)	0.39 (0.09–1.70)	−1.25	0 (0–85)	24.39 (9.17 to −38.46)	

Table 3 (*cont.*)

		N_{co}	ER_{IG} (95% CI)	ER_{CG} (95% CI)	RR (95% CI)	Z	I^2 (95% CI)	NNT/NNH (95% CI)[a]	p^b
Sex	Men	20	5.45 (3.24–9.03)	7.32 (4.75–11.12)	0.55 (0.26–1.17)	−1.56	0 (0–54)	40 (17.24 to −125)	0.68
	Woman	21	3.51 (2.35–5.21)	8.27 (6.01–11.28)	0.45 (0.26–0.78)	−2.84**	0 (0–52)	52.63 (25.64 to −2989.24)	
Education	Low (up to high school)	20	10.15 (5.34–18.45)	6.34 (2.66–14.45)	1.72 (0.53–5.61)	0.90	0 (0–79)	−30.30 (26.32 to −9.62)	0.03
	Moderate/high (high school+)	21	3.66 (2.41–5.50)	8.07 (6.09–10.63)	0.39 (0.22–0.68)	−3.30***	0 (0–55)	31.25 (19.23 to 76.92)	

N_{co}, Number of comparisons; ER, event rate (number of patients with reliable deterioration); IG, intervention group; CG, control group; RR, relative risk for a deterioration; RCI, Reliable Change Index; BDI, Beck Depression Inventory; CES-D, Centre for Epidemiological Studies Depression Scale; MDD, major depressive disorder; CBT, cognitive behavioural therapy.

[a] A negative number in the column NNT/NNH indicates numbers needed to harm. A positive number indicates numbers needed to treat.

[b] The *p* value indicates whether differences between subgroups are significant.

[c] 95% CI around I^2 cannot be calculated as there must be at least three studies with patients experiencing a reliable deterioration to calculate 95% CIs.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, † $p < 0.1$.

to avoid one additional deterioration was 43.21 (95% CI 25.83–132.10). Heterogeneity was zero. The risk of a deterioration from baseline to follow-up I (1–4 months) appeared to demonstrate a trend towards being lower in the intervention groups compared to the control groups (RR 0.47, 95% CI 0.20–1.42), although the difference did not reach statistical significance ($p = 0.097$). There were no significant differences between the groups in the relative risk of a deterioration from baseline to follow-up II ($p = 0.72$). Heterogeneity was zero at both follow-ups.

Sensitivity and subgroup analyses are presented in Table 3. Applying the alternative deterioration criteria (50% symptom increase) resulted in slightly lower deterioration rates, but demonstrated a similar overall pattern.

Effects of Internet-based treatments compared to control conditions on deterioration rates at post-treatment were non-significant ($p > 0.05$) in 11 out of 25 subgroups tested and showed significantly better outcomes for those in Internet-based treatment in 14 out of 25 subgroups tested. RR was higher among those in Internet-based treatments than those in control conditions in only one subgroup (i.e. those with low education), although this difference was not significant (RR 1.72, NNH 30.3, 95% CI −26.32 to 9.62, $p = 0.37$).

Moderator of deterioration effects

Education level was also the only significant moderator of treatment effects on deterioration, such that there was significantly higher risk for deterioration for participants with lower levels of educational attainment compared to those with more education. All other differences between subgroups on deterioration rates were non-significant ($p > 0.10$).

Benefit–risk ratio

Participating in Internet-based treatments for depression was not associated with an increased risk for deterioration when compared to a control group. There was only one subgroup analysis (i.e. participants with low levels of education) in which the relative risk for a deterioration was higher in the intervention group compared to the controls, although this difference was non-significant. Nonetheless, analyses of response rates at post treatment for the subgroup of participants with low education showed that their responses to treatment were significantly higher in the intervention group compared to controls, with a relative risk of 1.91 and a NNT to achieve one additional response of 3.23) (Ebert *et al.* unpublished data). Dividing the NNH in order that one symptom deterioration occurs through the NNT to achieve one treatment response, results in a benefit–risk ratio of 9.38, indicating that 9.38 participants with low education

achieved a treatment response compared to the control group for each participant experiencing a deterioration in symptoms.

Publication bias

Inspection of the funnel plot and Egger's test indicated some possible publication biases. However, adjustment for publication bias using Duval & Tweedie's trim-and-fill procedure did not result in substantial changes. After adjustment for missing studies (five imputed studies) the RR for deterioration by post-test was 0.58 (95% CI 0.38–0.90), NNT were 43.21 (95% CI 25.83–132.10). Results at both follow-ups stayed the same.

Discussion

This IPDMA evaluated deterioration rates of Internet-based guided self-help interventions for depression compared to control conditions in randomized trials. In addition, deterioration rates were evaluated in subgroups of interest and potential moderating effects were examined.

Results showed that overall deterioration rates were low and the risk of deterioration was significantly lower for participants in Internet-based guided self-help conditions compared to controls. Education significantly moderated the risk for deterioration such that participants with lower educational attainment displayed a higher risk of deterioration compared to participants with more education. Nonetheless, a risk–benefit ratio analysis indicated that also in the subgroup of participants with low education the likelihood of benefits of positive response to Internet-based treatment clearly outweigh the possible risk for deterioration.

To the best of our knowledge, the present study is the first meta-analysis that evaluated deterioration effects and its moderators in RCTs evaluating a psychological treatment. Observed deterioration effects are in the lower range (3.6%) of those found in observational studies of face-to-face psychotherapy (3–14%) (Strupp *et al.* 1977; Mohr, 1995; Hansen *et al.* 2006; Lambert *et al.* 2006). In contrast to early indications of possible adverse effects of psychological treatments (Bergin, 1966; Garfield *et al.* 1971), we did not find a deterioration effect as a consequence of therapy. Instead results indicate that participating in Internet-based guided self-help programmes is associated with a lower risk of deterioration (RR 0.47) relative to controls. This effect held for the overall group and most subgroups. However, education level was identified as a significant moderator, with low educated participants at a greater risk for a deterioration than highly educated participants. This finding corresponds to results from some randomized trials that found that lower educational attainment was associated with worse treatment outcomes compared to higher educated participants in Internet-based self-help interventions (Spek *et al.* 2008; Warmerdam *et al.* 2013). An explanation for such findings may be, that some patients with a lower educational level experience difficulties in terms of understanding the treatment modules, as most self-help manuals require a quite advanced reading comprehension. That may, in turn, decrease their self-efficacy and create feelings of hopelessness. Although all trials involved some form of guidance, this kind of support might not be sufficient for some individuals to overcome the barrier of low education. A more intensive treatment modality, as seeing a therapist face-to-face instead, could potentially help these patients understand the treatment rationale, and, thus, result in (hypothetically) less deterioration (Martinez *et al.* 2007). However, given that the topic of predictors of deterioration in psychotherapy has so far not been addressed in face-to-face psychotherapy, future studies should examine whether participants with a high risk for deterioration in Internet-interventions would be better suited for face-to-face psychotherapy. Another explanation may be that people with low education may also have other confounds (e.g. low income, poor physical health status, physical comorbidities, lower social support, less access to health services, etc.) which may either contribute to increased severity or lower ability to engage with the content/practice of skills from these programmes.

It should be noted, however, that deterioration rates of participants with low education (10%) were still in the range of those found in observational studies on face-to-face psychotherapy (3–14%, see above). Further, the benefit–risk ratio indicates that, in comparison to the control group, 9.38 patients with low education achieve a treatment response compared to the control group for each participant experiencing a deterioration in symptoms. It is also of note that with regard to response *v.* deterioration, a previously reported study using the same dataset did not find that education was a moderator of treatment response. Patients with low levels of education profited significantly and to almost the same extent (NNT = 3.23 for response) as patients with more education (NNT = 3.25 for response; Ebert *et al.* unpublished data). Thus, it is clear that most with low education experience response rather deterioration in Internet-based treatment. Therefore, low education alone should not be used to identify someone as high risk for deterioration and further research is needed to more specifically identify those who may be at high risk for deterioration.

When interpreting results from this study, several limitations need to be considered. First, the only negative effect evaluated was depression symptom deterioration. Other adverse effects may also occur and should be examined alongside RCTs in the context of

Internet-based guided self-help interventions in the future. For example, providing less intensive treatment than necessary through a self-help intervention might lead to lower treatment expectation in participants who fail to achieve a treatment response (Ebert *et al.* 2014*a*). Hence, although the present study did not find indications for harm of Internet-based guided self-help interventions, the study design does not allow to conclude an absence of harm. For a complete discussion on negative effects in Internet-based psychotherapy see Rozental *et al.* (2014) and for psychological treatments in general see Linden (2013). Future studies should examine other potential harmful effects of Internet-based treatments alongside RCTs. Second, given the limited number of studies that included a follow-up assessment, both for the intervention and the control condition, the analyses were underpowered to adequately conduct subgroup and moderator analyses at follow-up. Third, although the total number of participants was very high (2079), the low number of participants per subgroup did not allow for an examination of the association between the intervention and participant-characteristics within subgroups. For example, given the result for education as a moderator, future studies should investigate predictors of deterioration in the subgroup of participants with low levels of education in order to differentiate between those participants with low education with high chances for treatment success and participants with low education at high risk for failure. Moreover, all programmes were only examined in one randomized trial. Hence we were not able to investigate potential negative effects of specific programmes, which should be done in future studies. Fourth, the present study only investigated guided treatments for depression, hence we can not conclude anything about potential negative effects of unguided self-help treatments. Fifth, given the nature of IPDMA, the examined moderators of outcome were limited to those assessed in the original randomized trials. There might be other relevant moderators that have been not assessed.

The present study has relevant implications for both clinical practice and research. First, the differential results for moderators of effects on deterioration and treatment response indicate that the chances and risks for positive and negative change in psychological treatments might be two distinct constructs. Thus future studies on the differential effectiveness of psychological treatments should investigate moderators of both outcomes separately, instead of only evaluating the effects on mean change scores as is commonly done in psychotherapy research. Second, while many healthcare systems hesitate to implement Internet-based guided self-help approaches, the present study indicates, that such interventions are not associated with an increased risk for deterioration, but instead reduces the risk for a further aggravation of symptoms. Taken together with findings showing that such interventions have substantial positive effects on mean symptom improvement and on treatment response and remission (Johansson & Andersson, 2012; Ebert *et al.* 2015*b*) this further supports the need for dissemination of such treatments in routine mental health care. Nevertheless the moderator result for education indicates that a monitoring of participants with low education seems warranted, as they face an increased risk to deteriorate compared to participants with high education. Given that most participants with low education nevertheless achieve treatment response, and the mean effects on treatment response are comparable to those of participants with higher education, low education should not be used as an exclusion criteria in clinical practice. Instead, therapists should closely monitor the treatment and symptom progress in order to detect and react to early signs of a deterioration, e.g. by referral to more intensive treatment modalities. Given that the present study is the first study on deterioration rates in RCTs, one cannot conclude yet, whether these results are specific for Internet-based guided self-help intervention or whether such findings refer to psychological treatments for depression in general. Thus, future studies should evaluate deterioration rates and their moderators for face-to-face psychotherapy and should also compare overall and differential deterioration effects of internet-based and face-to-face psychotherapy.

The present study did not show any evidence for harm of Internet-based guided self-help interventions and indicates that such interventions reduce the risk for a symptom deterioration.

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Declaration of Interest

None.

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