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# „Der Effekt von Antidepressiva auf die Lebensqualität von depressiven Patienten – Eine systematische Literaturrecherche und Metaanalyse von Placebo-kontrollierten Studien“

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Professor Dr. med. Christopher Baethge
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Die Forschungsfrage zu dieser Arbeit stammt von Prof. Baethge, welcher dem Projekt während des gesamten Zeitraums beratend zur Seite stand.
Die Literaturrecherche, Artikelauswahl und Datenextraktion habe ich selbst vorgenommen. Parallel dazu hat Stefanie Kremer dieselbe Datenextraktion vorgenommen. Die Auswertung und Interpretation der Daten nahm ich gemeinsam mit Prof. Baethge vor, wobei wir Unterstützung von Dr. Bschor vom Institut für Psychiatrie und Psychotherapie der Technischen Universität Dresden erhielten.

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Wien, 06.02.2025

Teresa Wiesinger

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## INHALTSVERZEICHNIS

# ABKÜRZUNGSVERZEICHNIS

| | |
|---|---|
| AWM | Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften |
| BDI | Beck Depression Inventory |
| CMA | Comprehensive Metaanalysis |
| DSM | Diagnostic and Statistical Manual of Mental Disorders |
| EMA | European Medicines Agentur |
| FDA | Food and Drug Administration |
| HDRS | Hamilton Depression Rating Scale |
| HRQOL | Health related Quality of Life |
| ICD-10 | International Classification of Diseases 10. Edition |
| ITT | Intention to Treat |
| Q-LES-Q | Quality of Life Enjoyment and Satisfaction Questionaire |
| QOL | Quality of Life |
| MAO-Hemmer | Monoaminoxidasehemmer |
| MADRS | Montgomery Asberg Depression Rating Scale |
| MDD | Major Depressive Disorder |
| PRO | Patient Reported Outcomes |
| RCT | Randomized Controlled Trial |
| ROB | Risk of Bias |
| SF-36 | Short Form – 36 |
| SSRI | Serotonin-Rückaufnahme-Inhibitoren |
| SMD | Standardisierte Mittelwertsdifferenz |
| TZA | Trizyklische Antidepressiva |
| WHO | World Health Organisation |
| 95% CI | 95% Konfidenzintervall |

## 1. ZUSAMMENFASSUNG

Diese Arbeit beschäftigt sich mit der Frage, ob sich mit pharmakologischer Therapie durch Antidepressiva die subjektive Lebensqualität „Quality of life“ (QOL) von Patienten mit nachgewiesener Depression verbessern lässt.

Die Major Depression (MDD) hat eine hohe Prävalenz und kann unterschiedliche Verlaufsformen und Komponenten aufweisen. Laut Leitlinie ist die medikamentöse Behandlung ein wichtiger Bestandteil der Therapie der Depression, wobei Serotonin-Rückaufnahme-Inhibitoren (SSRI) die am häufigsten verschriebene Substanzklasse darstellen. Seit einem Paradigmenwechsel in Richtung Patient Reported Outcomes (PRO) ist QOL als sekundärer Endpunkt bei Antidepressiva-Studien fest etabliert. QOL ist kein scharf definierter Begriff, sondern vielmehr ein Überbegriff für viele unterschiedliche Konzepte und lässt sich mit einer Bandbreite an teilweise auch krankheitsspezifischer Fragebögen erheben.

Durch eine systematische Literaturrecherche in drei verschiedenen Datenbanken wurden statistische Daten von in randomisierten, placebokontrollierten Studien (RCTs) erhobener QOL-Werte gewonnen. Anschließend wurde eine random-effects Metaanalyse durchgeführt und die Effektstärke von QOL vs. Placebo errechnet. Diese beträgt 0.2 Standardized Mean Difference (SMD), zusätzlich wurden mehrere Subgruppenanalysen berechnet.

Auf Grundlage dieser Berechnungen haben wir ein Paper verfasst, welches Anfang 2023 unter dem Titel: „Antidepressants and quality of life in patients with major depressice disorder – Systematic review and meta-analysis of double-blind, placebo-controlled RCTs” in Acta Psychiatrica Scandinavica veröffentlicht wurde.

In Zusammenschau der Ergebnisse der Metaanalyse lässt sich nachweisen, dass Antidepressiva einen, wenn auch kleinen Effekt auf die Lebensqualität haben der sich in der Subgruppenanlyse verändert. Die Art und Weise, wie QOL derzeit bewertet wird, liefert nur begrenzte Informationen zum Wohlbefinden depressiver Patienten über die symptomatische Genesung hinaus.

## 2. EINLEITUNG

Depression ist eine Erkrankung von hoher Prävalenz, welche viele Lebensbereiche eines Patienten betreffen kann. Besonders die Lebensqualität, im Weiteren auch als „Quality of Life“ oder „QOL“ bezeichnet, kann dadurch massive Einschränkung erfahren.

Die Wirksamkeit von verschiedenen Antidepressiva wird in unzähligen Studien untersucht. Als Therapieerfolgskontrolle werden häufig in erster Linie Fremdbeurteilungsskalen zur Ermittlung der Schwere der Depression wie z. Bsp. die Hamilton-Skala[1] oder das Beck-Depressionsinventar[2] herangezogen.

Bereits seit den siebziger Jahren hat sich die subjektive Messung von QOL als sekundärer Endpunkt in Antidepressiva-Studien etabliert. Dadurch kann neben dem Therapieziel der Symptomreduktion auch der Einfluss der Depression auf das Leben des Patienten und die Gesellschaft erhoben werden[3].

### 2.1 Depression

#### 2.1.1 Epidemiologie und Einordnung

Depression ist heute die häufigste, psychiatrische Erkrankung weltweit und damit ständiger Gegenstand der medizinischen Forschung. Allein zwischen 1990 und 2017 ist die Prävalenz um 49.86% angestiegen, wobei regionale Unterschiede zu berücksichtigen sind[4].

Die groß angelegte „Global Burden of Disease Study“ gibt für das Jahr 2017 Depression als weltweit dritthöchsten Grund für gesundheitliche Einschränkung überhaupt an[5].

Immer jüngere Patienten haben einen Onset einer depressiven Episode, was vermutlich nicht zuletzt auf die speziellen Anforderungen der modernen Gesellschaft und deren fortschreitende Isolation zurückzuführen ist[6]. Die hohe Prävalenz von Adipositas und Nährstoffmangel der modernen, westlichen Ernährung könnten ebenfalls eine Rolle spielen[6].

Allein in Deutschland erkranken jährlich etwa 4.4 Millionen Menschen[7].

Frauen sind dabei etwa doppelt so häufig betroffen wie Männer. Es ist nicht ausreichend geklärt, wie dieser geschlechterspezifische Unterschied entsteht. Da die Prävalenz der Frauen sich nach der Menopause der der Männer angleicht, wird eine Rolle zyklischer Hormonschwankungen auf die an Stimmung und Verhalten beteiligten Hirnregionen wie Hippocampus und praefrontalen Cortex diskutiert. Psychosoziale und gesellschaftliche

Faktoren scheinen ebenfalls mitverantwortlich zu sein[8]. Je niedriger der sozioökonomische Status (zusammengesetzt aus Einkommen und Bildungsgrad), desto höher die Wahrscheinlichkeit an einer Depression zu erkranken[9].

Die Folgen sind gravierend. Erkrankte haben ein 40-60% höheres Risiko frühzeitig zu sterben, da sie unter anderem somatische Komorbiditäten wie kardiovaskuläre Erkrankungen oder Tumore vernachlässigen. Suizid ist nach wie vor weltweit die häufigste Todesursache junger Menschen und Hauptursache für die erhöhte Mortalität der Erkrankung[10].

### 2.1.2. Einteilung und Symptomatik

Die Einschlusskriterien der systematischen Literaturrecherche umfassten das Vorliegen einer Major Depression, im Folgenden auch als Major Depressive Disorder (MDD) bezeichnet. Laut DSM-IV [11] liegt eine depressive Episode einer Major Depression vor, wenn:

(A) Mindestens 5 von 9 im DSM-V gelisteten Symptomen über einen Zeitraum von 2 Wochen bestehen, welche eine Änderung gegenüber dem vorbestehendem Funktionsniveau darstellen, mindestens ein Symptom ist entweder depressive Verstimmung oder Verlust an Interesse oder Freude

(B) Die Symptome verursachen in klinisch bedeutsamer Weise Leiden oder Beeinträchtigungen in sozialen, beruflichen oder anderen Wichtigen Funktionsbereichen

(C) Die Symptome sind nicht Folge der physiologischen Wirkung einer Substanz oder eines medizinischen Krankheitsfaktors

Dabei sind folgende Ausschlusskriterien zu beachten:

(D) Das Auftreten einer Episode einer MDD kann nicht besser durch eine Schizoaffektive Störung, Schizophrenie, Schizophrenieforme Störung, Wahnhafte Störung oder Andere näher oder nicht näher Bezeichnete Störung aus dem Schizophrenie-Spektrum und Andere Psychotische Störungen erklärt werden.

(E) Es bestand niemals eine manische oder hypomane Episode.

Zusätzlich unterscheidet das DSM-V zwischen einer Einzelnen oder rezidivierenden Episoden, unterschiedlichen Schweregraden (Leicht-, Mittel- und Schwergradig), Status der Remission

(Teil- oder Vollremittiert), dem Vorliegen von psychotischen Merkmalen, sowie weiteren Spezifikationen (z.Bsp. Mit Angst oder saisonalem Beginn)[11].

### 2.1.3 Medikamentöse Behandlung der Depression

In Deutschland sind viele unterschiedliche Substanzklassen zur Behandlung der Depression zugelassen, wobei die meisten eine intrasynaptische Erhöhung von Serotonin und/oder Noradrenalin erreichen sollen[12]. Die gängigsten dieser Substanzklassen sind beispielsweise selektive Serotonin-Rückaufnahme-Inhibitoren (SSRI), selektive Serotonin-/Noradrenalin-Rückaufnahme-Inhibitoren (SSNRI), Tri- und tetrazyklische Antidepressiva (TZA) sowie Monoaminooxidase-Inhibitoren (MAO-Hemmer). Im Folgenden werden der Einfachheit halber all diese Substanzklassen unter dem Sammelbegriff „Antidepressiva" zusammengefasst.

Die AWMF-Leitline zur unipolaren Depression sieht eine allein auf medikamentösen Ansätzen beruhende Behandlung jedoch als nicht ausreichend[12]. Sie empfiehlt daher „grundsätzlich die Einbettung einer medikamentösen Therapie in ein therapeutisches Gesamtkonzept, das heißt eine Grundversorgung mit niedrigintensiven gesprächsbasierten Interventionen, die zusätzlich mit unterstützenden Maßnahmen und psychosozialen Interventionen kombiniert werden können"[12].

## 2.2 Quality of Life

### 2.2.1. Definition und Skalen

"What is the harmony within a man, and between a man and his world – the quality of life – to which the patient, the physician, and society aspire?"

Mit dem oben genanntem Zitat wird QOL von Elkinton et al[13] in einem Artikel über Transplantationsmedizin zum ersten Mal in der medizinischen Fachliteratur beschrieben. Seit den siebziger Jahren erscheint der Begriff in immer mehr Publikationen und wird

fachbereichsübergreifend zur subjektiven Beurteilung der Schwere von Erkrankungen hinzugezogen.

Ein Problem bei der Definition stellt dabei die Uneinheitlichkeit des Begriffs und nicht zuletzt der Bedeutung von QOL dar. Lebensqualität ist sehr individuell, krankheitsspezifisch und somit als Überbegriff für eine Fülle von Konzepten zu betrachten. Diese Diversität schlägt sich auch in der großen Zahl von unterschiedlichen Messinstrumenten nieder, welche deren Ergebnisse untereinander schwerer vergleichbar machen[14]. So erfragt der Kidney Disease Quality of Life (KDQOL) zur Erfassung der Lebensqualität von Dialysepatienten die Nierenfunktion[15], während beispielsweise der Diabetes-39 Probleme bei der Blutzuckermessung einschließt[16].

In den meisten klinischen Studien zur Wirksamkeit von Antidepressiva wird der Schweregrad der Depression als primärer Endpunkt bestimmt wird. Dazu werden bewährte Messinstrumente wie die Hamilton-Skala[1], das Beck-Depression-Inventory[2] oder die Montgomery-Asberg-Skala[17] eingesetzt. Dabei handelt es sich um Fremdbeurteilungsskalen, die durch den Untersucher ausgefüllt werden. Beispielweise fragt der Untersucher bei Erhebung der Hamilton-Skala nach depressiver Stimmung, Schuldgefühlen oder Schlafstörungen, welche symptomatisch für die MDD sind[1].

Die Erfassung von QOL als sekundären Endpunkt ermöglicht eine Erhebung des subjektiven Krankheitsempfinden, da die meisten Fragebögen vom Patienten selbst ausgefüllt werden. So umfasst der in unserer Studie häufig erhobene Short-Form-36 (SF-36) acht Dimensionen von Gesundheit[18]:

- Vitalität
- Körperliche Funktionsfähigkeit
- Körperliche Schmerzen
- Allgemeine Gesundheitswahrnehmung
- Körperliche Rollenfunktion
- Emotionale Rollenfunktion
- Soziale Funktionsfähigkeit
- Psychisches Wohlbefinden

Während die Erfassung der subjektiven Erfahrung in der somatischen Medizin lange vernachlässigt wurde, kann Sie in der Psychiatrie z.Bsp. durch depressive oder manische

Symptome zu Verzerrungen führen und ist immer im Kontext der Grunderkrankung zu betrachten[14].

### 2.2.2. Paradigmenwechsel und Patient Reported Outcomes

Laut der WHO ist Gesundheit „ein Zustand des vollständigen körperlichen, geistigen und sozialen Wohlergehens und nicht nur das Fehlen von Krankheit oder Gebrechen“[19]. Doch aus welcher Perspektive messen wir die Gesundheit eines Patienten?

In den letzten Jahrzehnten hat dahingehend in der medizinischen Forschung ein Paradigmenwechsel stattgefunden, weg von Parametern der Krankheitsaktivität, hin zum vom Patienten subjektiv wahrgenommenem Gesundheitszustand. Patient Reported Outcomes (PRO) sollen die Perspektive des Patienten in die klinische, epidemiologische und gesundheitsökonomische Forschung einschließen[20]. Es gibt Grund zur Annahme, dass PRO neben ihrer Relevanz als sekundärer oder primärer Endpunkt in wissenschaftlichen Studien bei regelmäßiger Anwendung in der klinischen Praxis wertvolle Informationen für die Diagnostik von z.Bsp. psychischen Komorbiditäten bei somatischen Erkrankungen oder der Therapieerfolgskontrolle liefern könnten. Aktuell scheint das Interesse an der Implementierung von PRO in die Patientenversorgung jedoch noch ein akademisches, welches noch nicht im täglichen Gebrauch angekommen ist [21].

Durch die steigende Zahl an klinischen Studien die PRO als Endpunkte einschließen, haben die US-Amerikanische Zulassungsbehörde Food and Drug Administration (FDA) und die Europäische Arzneimittelbehörde (EMA) im Bestreben deren Verwendung möglichst zu standardisieren jeweils Guidelines herausgegeben[22-24].

Laut der FDA wird ein PRO als nicht von außen beeinflusste, direkt vom Patienten kommende Aussage über den Gesundheitszustand, die als Effektmaß in klinischen Studien verwendet werden kann, definiert[23]. Das im Zentrum dieser Arbeit stehende QOL kann als Konzept den PRO zugeordnet werden.

PRO kann nach zwei Ansätzen gemessen werden[25]:

1.) psychometrischer Ansatz: fasst unterschiedliche Dimensionen (erlebte Symptome, Emotionen, Verhaltensweisen) zu einem komplexeren Konzept zusammen
2.) präferenzbasierter Ansatz: misst den Wert, den der Patient einem bestimmten Gesundheitszustand beimisst

PRO-Konzepte können spezifische Informationen über definierte Patientenpopulationen liefern, jedoch nicht über Krankheitsgrenzen hinweg – dies wird erst durch die Verwendung von generischen Messmethoden möglich, vermutlich zu Kosten der Präzision[25].

### 2.2.3. Stand der Forschung

Obwohl sich QOL wie oben beschrieben in der Antidepressiva-Forschung bereits als sekundärer Endpunkt etabliert hat, gab es bisher nur wenige systematische Übersichtsarbeiten zu diesem Parameter, welche sich, respektive der unterschiedlichen Kohorten, auch widersprechen.

Stevanovic et al untersuchten den Einfluss antidepressiver Therapie auf Kinder und Jugendliche mit Depression oder Angststörung. In dem durch den Einschluss von nur fünf passenden Studien limitierten Review konnte kein eindeutiger Effekt von Antidepressiva auf QOL in dieser Patientengruppe gefunden werden[26].

Eine größer angelegte Übersichtsstudie von Ishak et al die den Einfluss von Pharmako- und Psychotherapie verglich, konnte einen durchaus positiven Einfluss auf QOL feststellen, besonders in deren Kombination[27]. Ein moderater Effekt wird auch in einer anderen Metaanalyse, die beide Behandlungsmethoden untersuchte, beschrieben. Die Autoren verweisen aber auf die unterschiedlichen Mechanismen, die zur Symptomreduktion und damit subjektiven Verbesserung der QOL führten[28].

2022 wurde eine Analyse der 17 Millionen Probanden umfassende US-amerikanischen Medical Expenditures Panel Survey veröffentlicht, von welchen 58% Antidepressiva erhielten. In der Auswertung der Daten des episodisch durchgeführten SF-36 Fragebogens konnte kein positiver Einfluss von antidepressiver Therapie auf QOL gefunden werden[29].

## 2.3 Ziel der Arbeit

Ziel dieser Arbeit ist es herauszufinden, ob eine Therapie mit Antidepressiva die subjektive Lebensqualität und damit den erhobenen QOL-score positive beeinflussen können.

In der Literatur findet sich keine Übersichtsarbeit, die diese Frage explizit im Kontext des Behandlungserfolgs von Antidepressiva bei einer nachgewiesenen Episode einer MDD beantwortet.

Die in einer systematischen Literaturrecherche gewonnenen Daten sollen mittels einer Metaanalyse ausgewertet werden. Dabei werden unterschiedliche Subgruppen, wie z.Bsp high/low Risk of Bias nebeneinander betrachtet werden, um ein breiteres Bild erhalten zu können. Anschließend sollen Ergebnisse kritisch und in den aktuellen Stand der Forschung eingebettet besprochen werden, um eine Aussage über den Effekt von Antidepressiva auf QOL machen zu können.

## 3. PUBLIKATION

**3.1 Wiesinger T, Kremer S, Bschor T, Baethge C. Antidepressants and quality of life in patients with major depressive disorder - Systematic review and meta-analysis of double-blind, placebo-controlled RCTs. Acta Psychiatr Scand. 2023 Jun;147(6):545-560. doi: 10.1111/acps.13541. Epub 2023 Mar 20. PMID: 36905396.**

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SYSTEMATIC REVIEW

Acta Psychiatrica Scandinavica WILEY

# Antidepressants and quality of life in patients with major depressive disorder – Systematic review and meta-analysis of double-blind, placebo-controlled RCTs

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**Abstract**

**Background:** Quality of Life (QoL) is an important outcome in mental disorders. We investigated whether antidepressant pharmacotherapy improved QoL vs. placebo among patients with MDD.

**Methods:** Systematic literature search in CENTRAL, Medline, PubMed Central, and PsycINFO of double-blind, placebo-controlled RCTs. Screening, inclusion, extraction, and risk of bias assessment were conducted independently by two reviewers. We calculated summary standardized mean differences (SMD) with 95%-CIs. We followed Cochrane Collaboration's Handbook of Systematic Reviews and Meta-Analyses and PRISMA guidelines (protocol registration at OSF).

**Results:** We selected 46 RCTs out of 1807 titles and abstracts screened, including 16.171 patients, 9131 on antidepressants and 7040 on placebo, a mean age of 50.9 years, with 64.8% women. Antidepressant drug treatment resulted in a SMD in QoL of 0.22 ([95%-CI: 0.18; 0.26] $I^2$ 39%) vs. placebo. SMDs differed by indication: 0.38 ([0.29; 0.46] $I^2$ 0%) in maintenance studies, 0.21 ([0.17; 0.25] $I^2$ 11%) in acute treatment studies, and 0.11 ([−0.05; 0.26], $I^2$ 51%) in studies focussing on patients with a physical condition and major depression. There was no indication of subtstantial small study effects, but 36 RCTs had a high or uncertain risk of bias, particularly maintenance trials. QoL and antidepressive effect sizes were associated (Spearman's rho 0.73, $p < 0.001$).

**Conclusions:** Antidepressants' effects on QoL are small in primary MDD, and doubtful in secondary major depression and maintenance trials. The strong correlation of QoL and antidepressive effects indicates that the current practice of measuring QoL may not provide sufficient additional insights into the well-being of patients.

KEYWORDS

antidepressives, meta analysis, quality of life, randomized controlled trial

## 1 | INTRODUCTION

Quality of life has become a key criterion in evaluating treatment success in medicine although it found its way into psychiatry only relatively late.[1,2] Today, however, QoL is a common secondary outcome in many RCTs of psychiatric pharmacotherapy, including antidepressant drug trials. Antidepressant efficacy and quality of life share common domains: SF-36,[3] probably the most widespread QoL scale, asks participants: „Have you felt so down in the dumps that nothing could cheer you up? "or „Have you felt downhearted and blue? "– questions clearly related to depressed mood items in depression rating scales, for example, item 1 in the Hamilton Rating Scale for Depression, HAM-D.[4] At the same time, quality of life is the more overarching concept of well-being and QoL scales typically cover aspects not primarily linked to depression, e.g., the ability to carry out everyday activities, such as lifting groceries.[2] Also, whereas most depression rating scales employed in studies are filled out by healthcare personal QoL scales usually are self-rating instruments. In sum, it is not a given that antidepressant drugs positively affect quality of life.

Results from single studies are equivocal: Heiligenstein and co-authors (1995), for example, in one of the earliest studies on QoL in antidepressant pharmacotherapy, found that fluoxetine improved quality of life relative to placebo in a group of patients diagnosed with late-life depression. In a more recent RCT, however, Gommol et al. (2013) reported only a negligible effect among outpatients with major depressive disorder treated with levomilnacipran as compared to placebo.

There exists a – negative – Cochrane review on antidepressants and quality of life[5] although it is restricted to SSRIs and to the topic of stroke recovery. In a comprehensive, but narrative review Ishak and co-authors concluded that both medication and psychotherapy have favorable effects on quality of life.[6] In a recent and much publicized analysis of data from the United States' Medical Expenditures Panel Survey, however, no positive influence of antidepressants on the health-related quality of life in participants with depression was found.[7]

We are not aware of summarizing and quantitative research on QoL regarding the whole range of antidepressant treatment in major depressive disorder. To address this gap, we have carried out a systematic literature search and a meta-analysis of antidepressant effects on quality of life in placebo-controlled randomized drug trials of antidepressant pharmacotherapy among patients with major depressive disorder.

**Summations**

- Antidepressant drug treatment positively affects QoL among patients with an episode of major depressive disorder, but only to a modest extent.
- Treatment effects on QoL and depression are highly correlated, probably because concepts overlap.
- Even though social functioning and depression also share certain domains, social functioning may be a more informative part of QoL to target in RCTs of patients with major depressive disorder.

**Limitations**

- While all scales included in this analysis converge on patient well-being, QoL is a heterogeneous construct.
- All results are based on study-level, not individual patient data.

## 2 | METHODS

The protocol of the present study has been pre-registered on the Open Science Framework webpage (https://osf.io/dvza6).[8] In conducting the literature search and the meta-analysis and in reporting its results we followed the Cochrane Handbook for Systematic Reviews of Interventions[9] and the PRISMA guidelines.[10]

## 3 | LITERATURE SEARCH

In our literature search, we applied no date nor language restrictions and did not exclude gray literature.

### 3.1 | Eligibility criteria

We searched for placebo-controlled, randomized trials of patients with depressive disorders that reported results on QoL.

### 3.2 | Inclusion criteria

- Diagnosis of major depressive disorder according to an established diagnostic instrument, e.g., as DSM-IV, −5, or ICD-10.

- Documentation of QoL data according to a quantitative tool, e.g., SF-36 (total score or subdomain score), Q-LES-Q, Satisfaction with life scale.
- Antidepressant drug treatment as the only specific psychopharmacologic therapy. For example, antidepressant combinations or augmentation of antidepressant drugs with antipsychotics or lithium were not included.
- QoL data available for both antidepressant and placebo arms

### 3.3 | Exclusion criteria

- Studies on antidepressant and QoL in other fields of depressive disorder research, e.g. stroke rehabilitation, migraine prophylaxis, treatment of acute pain.
- Studies focussing on social functioning rather than on quality of life, e.g. studies exclusively applying the Sheehan Disability Scale.[11]
- Studies on children and adolescents were excluded, otherwise there were no restrictions regarding age or gender.

### 3.4 | Information sources

We carried out searches in the Cochrane Central Register of Controlled Trials (CENTRAL), in NLM databases, specifically in Medline and PubMed Central (via PubMed), and in PsycINFO. Also, reference lists of review articles and of all papers eventually included were hand searched for additional studies.

### 3.5 | Search strategy

The literature search combined generic as well as specific terms for antidepressant drugs, randomized trials, and quality of life. We have detailed the search history in the study protocol and in Table S1. The last search of all databases was carried out in February 2023, the last date covered is December 31, 2022.

### 3.6 | Selection process

Two authors (TW, SK) independently screened all search hits on a title and abstract basis. We obtained full-texts of all studies potentially eligible for inclusion. If eligibilty remained unclear a final decision was made in a discussion with the senior author (CB).

## 4 | DATA COLLECTION

Two authors (TW, SK) independently extracted data from the studies included using a standardized Excel-form similar to those employed in earlier studies of our group.[12 – 16] Specifically, we collected information on number, gender, and age of participants, diagnosis, interventions, trial duration, psychometric instruments employed, results (point estimates and measures of dispersion), as well as meta-data regarding authors, journal, publication year, and funding source. We deemed a study funded by drug manufacturers if it was entirely or partly funded, sponsored, or supported by a pharmaceutical company. Also, we considered authorship affiliation with a company a proxy for funding – in contrast to merely positive COI statements. Wherever possible we selected intention to treat outcomes, and if results were available for several time points during follow up, we decided for the longest duration. All unclear cases were solved by discussion among the authors (TW, SK, CB).

Data available from graphs only were read out by means of Plot digitizer software.[17] If data were missing from original articles, we contacted authors via e-mail.

### 4.1 | Risk of bias

Two raters independently (TW, SK) assessed the risk of bias of all studies by means of the Cochrane Collaboration RoB tool[9] using the following items: Sequence generation, allocation concealment, blinding of participants and personel, blinding of outcome assessors, incomplete outcome data, selective reporting of outcomes, and other sources of bias (e.g., enriched design). A low risk of bias was assumed only if all domains were rated low, and studies were considered carrying a high risk of bias as soon as one domain was rated high. If no item was rated high but at least one item was uncertain the study was classified as having an uncertain risk of bias. All assessments were double-checked by the senior author (CB).

### 4.2 | Effect measures

Antidepressant effects on quality of life and depressive symptoms were calculated as standardized mean differences (Cohen's *d*) and 95%-confidence intervals between antidepressant drug and placebo arms, based on the changes from baseline (or, if not available, scores at follow-up) in the scales employed. We opted for change from baseline to account for differences between study arms at baseline. We searched for global measures of quality of life, such as SF-36's general health score[3] in

order to capture quality of life in its meaning as a measure of general well-being. If global measures were not provided we selected mental component scores of QoL instruments (e.g. SF-36's mental component). If more than one QoL instrument was employed in a RCT we prioritized widely used scales: SF-36 (or subscales) and then Q-LES-Q.[18]

For antidepressant drug effects on depression, we calculated standardized mean differences 95%-confidence intervals based on established rating scales for depression, such as HAM-D[4] or MADRS (Montgomery-Asberg Depression Rating Scale).[19] If several instruments were used in one study, for comparability, we prioritized HAM-D and then MADRS.

## 5 | DATA SYNTHESIS

The primary outcome in this study is the effect of antidepressants on quality of life, represented as standardized mean difference between drug and placebo arms and its 95%-confidence interval. As a secondary outcome, we computed effect sizes with regard to depression rating scales.

Following the Cochrane Collaboration's Handbook of Systematic Reviews and Meta-Analysis we calculated SMDs either based on follow-up figures only, on changes from baseline, or, if those results were not available, based on contingency tables, correlation coefficients, and p-values or other test variables (e.g., *t*-values). In the event of more than one verum arm being tested within one RCT, such as different antidepressant drugs or different doses of one drug, we combined arms to yield one comparison group and to avoid double-counting of patients in placebo groups. If standard deviations or standard errors were not provided in original papers, they were calculated from confidence intervals or p-values. In this analysis, we did not need to impute measures of dispersion from other studies.

Original studies were similar in design but not identical. Hence, summary estimates were calculated in random effects meta-analyses (DerSimonian and Laird). Results are displayed in forest plots. Heterogeneity is described by Q-statistics and $I^2$-values, representing the excess variance beyond random error. We also present prediction intervals to indicate the expected range of effects in populations comparable to those included in this meta-analysis.

### 5.1 | Reporting bias

We computed funnel plots and calculated Egger's test, in order to find evidence of small study effects.

### 5.2 | Sensitivity analyses

We calculated effect sizes for studies with low versus uncertain/high risk of bias studies.

### 5.3 | Subgroup analyses

We found three different kinds of trials in this literature search: 1. acute treatment trials among patients primarily diagnosed with major depressive disorder („primary depression"), 2. acute treatment trials among patients primarily diagnosed with somatic disorders, e.g., diabetes or heart failure, and secondary depression („secondary depression"), and 3. maintenance/continuation trials among patients with remitted depressive disorders. For simplicity, we refer to the last group of trials as maintenance trials although the studies by Perahia et al.[20] and Kamijima et al.[21] are continuation studies.

In a *posthoc analyses*, we therefore calculated meta-analyses according to those groups of studies.

We also compared studies testing global QoL measures, such as the SF-36 total score or Q-LES-Q, versus those focussing on mental health or depression related quality of life, such as SF-36 mental component score or the Quality of Life in Depression Scale (QLDS). Further, we analyzed RCTs by funding status. Finally, we calculated Spearman's rho of quality of life and depression SMDs as well as a bivariate meta-regression (weighted for study variance) of quality of life on antidepressant effect.

### 5.4 | Statistical analysis

Descriptive statistics are presented as means, medians or percentages, with standard deviations or ranges, as appropriate. We employed Jamovi, version 2.3, for calculating Spearman's rho and Wilcoxon's signed rank test and used Comprehensive Meta-Analysis, CMA, version 2, as well as the Campbell Collaboration's effect size calculator[22] for computing effect sizes. Meta-analyses and bivariate meta-regression were carried out in Comprehensive Meta-Analysis, CMA, version 2 and in CMA prediction intervals. Results are presented as summary estimates of standardized mean differences with 95% confidence intervals. Positive values of SMDs indicate superior effects of antidepressants.

## 6 | PICO RESEARCH QUESTION

To what extent is quality of life (O) improved by antidepressant drug treatment (I) relative to placebo (C) among patients diagnosed with major depressive disorder (P)?

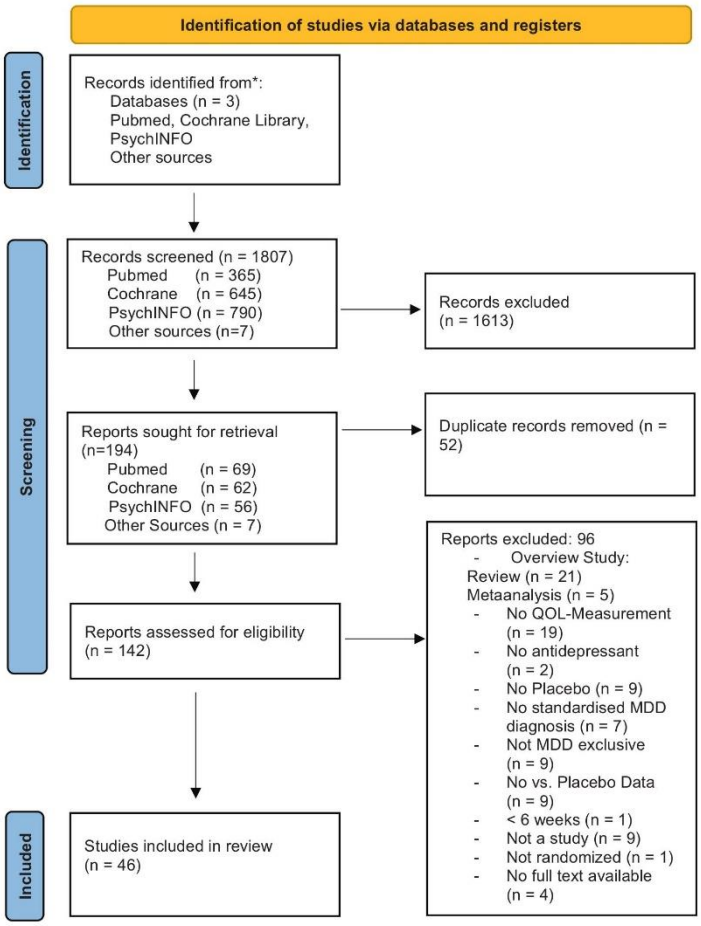


**FIGURE 1** PRISMA flowchart. (*no automation tools were used during screening)

## 7 | RESULTS

Out of 1807 titles and abstracts screened we selected 46 placebo-controlled RCTs.[20,21,23–66] For the purposes of this meta-analysis, Demyttenaere and co-authors' statistical combination of similar trials[61] was counted as one study although, technically, the summary result originates from four RCTs (e.g., Burke et al. 2002[67], to avoid double counting, has not been included as a single study). Figure 1 presents the PRISMA flowchart. In most studies *not included*, quality of life measures were not investigated, were not reported, or were not sufficiently reported.

The studies selected for meta-analysis were published between 1995 and 2019, included 16.171 patients at baseline, 9131 on antidepressants and 7040 in placebo arms, with an unweighted mean age of 50.9 years. 64.8% of participants were women. The quality of life instruments most often employed in the trials were the Quality of Life, Enjoyment, and Satisfaction Questionnaire, Q-LES-Q ($n = 13$), and the Short Form Health Survey, as SF-36 ($n = 11$) or SF-12 ($n = 1$). The dominant depression scales were HAM-D and MADRS.

Twenty-nine studies were acute treatment studies including patients diagnosed with a primary diagnosis of major depression (primary depression), 10 trials recruited patients with depressive syndromes during the course of another disorder, e.g. diabetes, chronic heart failure, or chronic kidney disease (secondary depression), and seven investigations were maintenance trials within which patients were not clinically depressed at study start. Invariably, the studies were double-blind. All studies, including their risk of bias, are summarized in Table 1.

TABLE 1 Study characteristics

| | Study | Year | Duration | acute/ maint. | n | Gender | Mean age | Comorbidity | Study drug | QOL | Severity of depression | Blinding of Participants | Risk of Bias |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **Angermann** | 2016 | 24 months | acute | 226 | f: 24% m: 76% | 62.2 (12.0) | Heart failure | Escitalopram 10–20 mg | KCCQ | MADRS PHQ-9 | Double blind | low |
| 2 | **Ashman** | 2009 | 10 weeks | acute | 41 | f: 41.5% m: 58.5% | 49.1 (10.9) | TBI | Sertraline 50–200 mg | Life-3 | HAM-D | Double blind | low |
| 3 | **Banerjee** | 2013 | 39 weeks | acute | 156 | f: 67.79% m: 32.21% | 79.33 (8.53) | Dementia | Sertraline 50 mg, Mirtazapine15 mg | Euroqol | CSDD (Cornell Scale for depression in dementia) | Double blind | low |
| 4 | **Baarge-Scharpveldt** | 2002 | 18 weeks | acute | 63 | f: 73% m: 27% | 34.4 | none | Imipramine 50–200 mg | SWLS | HAM-D | Double blind | unclear |
| 5 | **Blum** | 2014 | 8 weeks | acute | 514 | no info | no info | none | Levomilnacipran 40–120 mg | SF-36 | MADRS | Double blind | high |
| 6 | **Boulenger** | 2014 | 8 weeks | acute | 604 | w: 65.9% m: 34.1% | 46.57 (13.68) | none | Vortioxetine 15 mg, Vortioxetine 20 mg, Duloxetine 60 mg | Q-LES-Q | MADRS CGI-S | Double blind | low |
| 7 | **Boyer** | 2015 | 26 weeks | acute | 548 | w: 71.35% m: 28.65% | 45.65 (13.0) | none | Desvenlaflaxine 50 mg | WHO-5 | HDRS-17 | Double blind | high |
| 8 | **Clayton** | 2013 | 8 weeks | acute | 432 | w: 100% | 53.2 (6.8) | none | Desvenlaflaxine 50 mg | WHO-5 | HDRS, MADRS | Double blind | unclear |
| 9 | **Demyttenare** | 2008 | 8 weeks | acute | 1545 | f. 58.77% m: 41.23% | 40.28 (11.7) | none | Escitalopram 10–20 mg Citalopram 20–40 mg Escitalopram 10–20 mg Sertraline 50–100 mg | Q-LES-Q | MADRS | Double blind | unclear |
| 10 | **Detke 1** | 2002 | 9 weeks | acute | 236 | f: 67.08% m: 32.92% | 42.39 (13.15) | None | Duloxetine 60 mg | QLSD | HAM-D CGI-S | Double blind | unclear |
| 11 | **Detke 2** | 2002 | 9 weeks | acute | 267 | f: 68.91% m: 31.09% | 41 (14.05) | None | Duloxetine 60 mg | QLSD | HAM-D CGI-S | Double blind | unclear |
| 12 | **Dombrovski** | 2007 | 1 year | m/c | 116 | f: 64.66% m: 35.34% | 76.92 (5.74) | Age 70+ | Paroxetine 10–40 mg | HR-QoL | HAM-D | Double blind | High |
| 13 | **Dunlop** | 2011 | 12 weeks | acute | 427 | f: 65.81% m: 34.19% | 42.67 (12.02) | None | Desvenlaflaxine 50 mg | Q-LES-Q | MADRS HAM-D CGI | Double blind | unclear |
| 14 | **Echeverry** | 2009 | 6 months | acute | 89 | f: 73% m: 27% | 52.49 (9) | Diabetes | Sertraline 50–100 mg | Diabetes-39 | HAM-D | Double blind | unclear |
| 15 | **Fann** | 2017 | 12 weeks | acute | 62 | f: 24.19% m: 75.81% | 37 (12.5) | TBI | Sertraline 50–200 mg | SF-36, MCS | HAM-D | Double blind | low |
| 16 | **Goldstein** | 2004 | 8 weeks | acute | 353 | f: 61.47% m: 38.53% | 40.5 (11.5) | none | Duloxetine 40 mg Duloxetine 80 mg Paroxetine 20 mg | QLSD | HAM-D | Double blind | unclear |
| 17 | **Gommoll** | 2014 | 8 weeks | acute | 355 | f: 60.34% m: 39.66% | 43.26 (13.09) | none | Levomilnacipran 40–120 mg | SF-36, MCS | MADRS | Double blind | unclear |

TABLE 1 (Continued)

| | Study | Year | Duration | acute/ maint. | n | Gender | Mean age | Comorbidity | Study drug | QOL | Severity of depression | Blinding of Participants | Risk of Bias |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 18 | **Gottlieb** | 2007 | 12 weeks | acute | 28 | f:14.3% m: 85.7% | 62 (10.58) | Chronic Heart Failure | Paroxetine 12–25 mg | SF-36, GH | BDI | Double blind | high |
| 19 | **Hedayati** | 2017 | 12 weeks | acute | 193 | f: 26.94% m: 73.06% | 58.4 (13.39) | Chronic Kidney Disease | Sertraline 50–200 mg | KDQOL-SF, GH | QIDS-C16 | Double blind | low |
| 20 | **Heiligenstein** | 1995 | 6 weeks | acute | 532 | f: 53.76% w: 46.24% | 67.65 (5.61) | Age 60+ | Fluoxetine 20 mg | SF-36 GH | HAM-D | Double blind | High |
| 21 | **Hewett 1** | 2009 | 8 weeks | acute | 543 | f: 79.33% m: 20.67 | 42.09 (11.56) | none | Bupropion 150–300 mg, Venlaflaxine 75–150 mg | Q-LES-Q, LS | HAM-D MADRS CGI | Double blind | unclear |
| 22 | **Hewett 2** | 2010a | 10 weeks | acute | 418 | f: 72.01% m: 27.99% | 71.1 (5.75) | none | Bupropion 150–300 mg | Q-LES-Q, LS | HAM-D MADRS CGI | Double blind | unclear |
| 23 | **Hewett 3** | 2010b | 8 weeks | acute | 581 | f: 65.82% m: 34.18% | 44.75 (11.38) | none | Bupropion 150–300 mg, Venlaflaxine 75–150 mg | Q-LES-Q, LS | HAM-D MADRS CGI | Double blind | unclear |
| 24 | **Kamijima** | 2006 | 16 weeks | acute | 235 | f: 63% m: 37% | 40 | none | Sertraline 50–100 mg | Q-LES-Q | HAM-D CGI | Double blind | high |
| 25 | **Kim** | 2014 | 24 weeks | m/c | 217 | (no info) | (no info) | ACS | Escitalopram 5–20 mg | WHQOL-BREF „social relationships“ | BDI | Double blind | low |
| 26 | **Kocsis 1** | 2002 | 18 months | m/c | 161 | f: 66% m: 34% | 41.6 (9.4) | none | Sertraline 50–200 mg | SF-36 „role emotional“ | HAM-D CGI | Double blind | high |
| 27 | **Kocsis 2** | 2007 | 52 weeks | m/c | 258 | f: 65% m: 35% | 42,3 | none | Venlafaxine ER (75–300 mg) | Q-LES-Q | HAM-D CGI | Double blind | high |
| 28 | **Kornstein** | 2010 | 8 weeks | acute | 372 | f: 100% | 52.34 (6.36) | none | Desvenlaflaxine 50–100 mg | WHO-5 | HDRS, MADRS | Double blind | high |
| 29 | **Lewis** | 2019 | 12 weeks | acute | 527 | f: 59 & m: 41% | (no info) | none | Sertraline 50 mg | SF-12 MH | BDI-II CIS-R | Double blind | low |
| 30 | **Liebowitz 1** | 2007 | 8 weeks | acute | 234 | f: 60.26% m: 39.74 | 40.93 (12.71) | none | Desvenflaflaxine 100-200 mg | WHO-5 | HAM-D MADRS CGI | Double blind | unclear |
| 31 | **Liebowitz 2** | 2008 | 8 weeks | acute | 447 | f: 59.51% m: 40.49% | 42.66 (14.0) | none | Desvenlaflaxine 50 mg, Desvenlaflaxine 100 mg | WHO-5 | HAM-D MADRS | Double blind | unclear |
| 32 | **Liebowitz 3** | 2013 | 8 weeks | acute | 673 | f: 60.77%, m: 39.23% | 41.99 (13.68) | none | Desvenflaflaxine 10 mg, Desvenlaflaxine 50 mg | WHO-5 | HAM-D MADRS | Double blind | low |
| 33 | **Lydiard** | 1997 | 8 weeks | acute | 392 | f:30 66.58% m: 33.42% | 40.14 | none | Sertraline 50–200 mg, Amitryptiline 50–150 mg | Q-LES-Q, LS | HAM-D MADRS CGI | Double blind | unclear |

(Continues)

TABLE 1 (Continued)

| | Study | Year | Duration | acute/ maint. | n | Gender | Mean age | Comorbidity | Study drug | QOL | Severity of depression | Blinding of Participants | Risk of Bias |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 34 | **Perahia** | 2006 | 12 weeks | m/c | 269 | f: 72.66%<br>m: 27.34% | 45.24 (12.25) | none | Duloxetine 2x60 mg | QLSD | HAM-D<br>CGI-S | Double blind | high |
| 35 | **Phillipp** | 1999 | 8 weeks | acute | 151 | f: 75%<br>m: 25% | 47 (12) | none | Imipramine 100 mg | SF-36 MCS | HAM-D | Double blind | unclear |
| 36 | **Rapaport** | 2009 | 10 weeks | acute | 433 | f: 61,04%<br>m: 38.96% | 67.35 (6.49) | 60+ | Paroxetine 12,5 mg,<br>Paroxetine 25 mg | Q-LES-Q | HAM-D | Double blind | unclear |
| 37 | **Rouillon** | 2000 | 1 year | acute | 203 | f: 66.67%<br>m: 33.33% | 45 | none | Milnacipran 50 mg | DIP | HDRS<br>CGI | Double blind | high |
| 38 | **Schneider** | 2003 | 8 weeks | acute | 728 | f: 56.04%<br>m: 43.96% | 69.8 (6.65) | 60+ | Sertraline 50–100 mg | SF-36 GH | HAM-D<br>CGI | Double blind | unclear |
| 39 | **Stahl** | 2009 | 8 weeks | acute | 482 | f: 65.41%<br>m: 34.59% | 43.34 (12.29) | none | Agomeltain 25 mg,<br>Agomeltin 50 mg | QLDS | HAM-D<br>CGI | Double blind | unclear |
| 40 | **Swenson** | 2003 | 24 weeks | acute | 337 | f: 63.49%<br>m: 36.51% | 57.2 (10.75) | Post ACS | Sertraline 50–200 mg | Q-LES-Q | BDI | Double blind | unclear |
| 41 | **Thase** | 2016 | 8 weeks | acute | 372 | f: 65.5%<br>m: 34.5% | 44.75 (13.54) | none | Levomilnacipran 20-120 mg | SF-36 | MADRS | Double blind | unclear |
| 42 | **Trivedi** | 2004 | 8 weeks | acute | 387 | f: 58.37%<br>m: 41.63% | 38.8 (11.53) | none | Paroxetine 12,5 mg<br>Paroxetine 25 mg | Q-LES-Q | HAMD | Double blind | unclear |
| 43 | **Weintraub** | 2010 | 12 weeks | acute | 131 | f: 54%<br>m: 46% | 79 | Alzheimers Disease | Sertraline 50–100 mg | ADRQL | CSDD | Double blind | low |
| 44 | **Wise** | 2007 | 8 weeks | acute | 311 | no info | no info | Age 65+ | Duloxetine 60 mg | SF-36 MCS | HAM-D | Double blind | high |
| 45 | **Zajecka** | 2010 | 8 weeks | acute | 417 | f: 66.7%<br>m: 33.3% | 43.8 (12.22) | none | Agomelatine 25 mg,<br>Agomelatine 50 mg | QLDS | HAM-D | Double blind | unclear |
| 46 | **Zilcha-Mano** | 2013 | 16 weeks | acute | 105 | f: 59%<br>m: 41% | 37.5 (12.2) | none | Sertraline<br>Venlaflaxine | Q-LES-Q | BDI | Doubel blind | low |

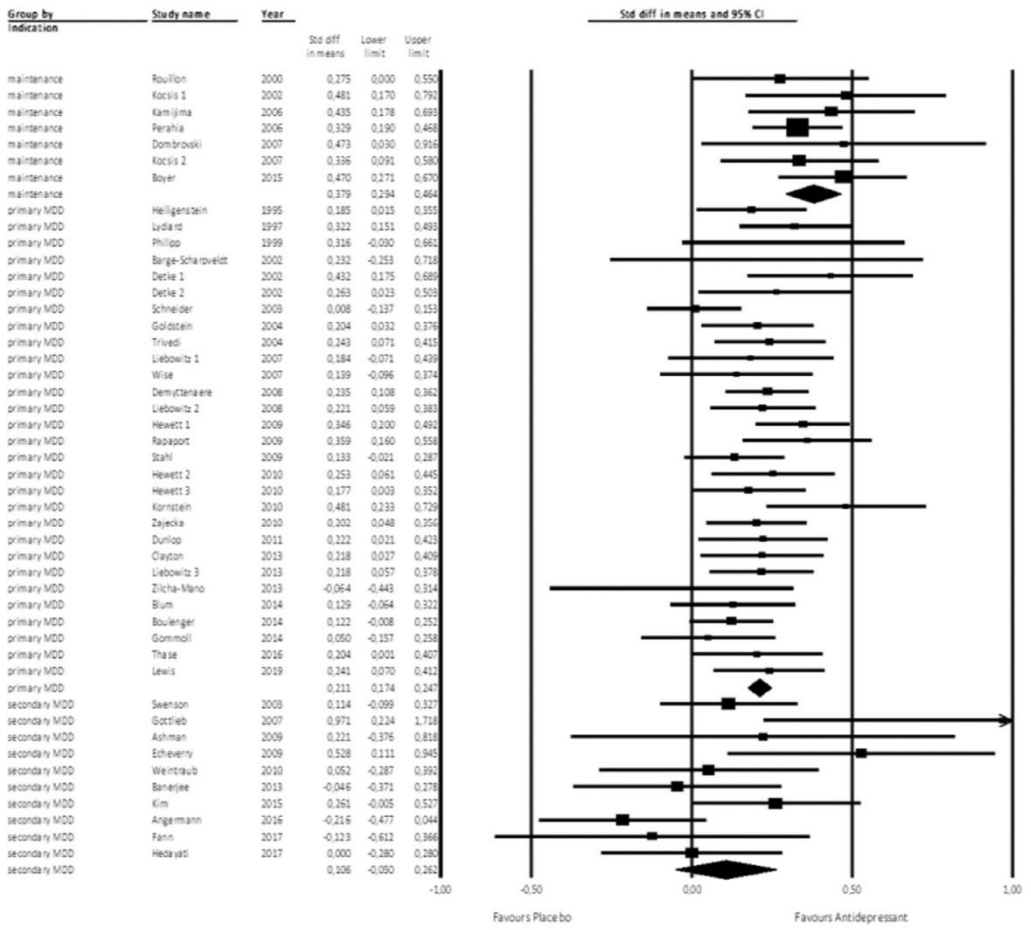


**FIGURE 2** Forest plot of random-effects meta-analyses of maintenance treatment and of acute treatment of primary as well as secondary depression. (Legend: $N = 46$ double-blind, placebo-controlled randomized trials, positive values indicate superiority of antidepressants)

## 8 | PRIMARY OUTCOME

The summary effect of antidepressants on quality of life in comparison to placebo across all 46 RCTs was 0.22 SMD ([95%-CI: 0.18; 0.26] $I^2$ 39%), with a 95%-prediction interval ranging from 0.05 to 0.40. SMDs were lower in studies with low as opposed to those with high/uncertain risk of bias: 0.11 [0.01; 0.20] vs 0.25 [0.20; 0.29] (Q: 7.0, $p = 0.008$). Egger's test ($p = 0.51$) and a funnel plot gave no indication of small study effects (publication bias), and a trim and fill analyses resulted in only a marginal difference. There were too few maintenance studies to allow for an analysis of small study effects in this subgroup. When we removed one study at a time no signal of undue reliance on any single study emerged.

*Posthoc* analyses revealed that summary effects differed statistically significantly by indication ($p = 0.001$; df(Q): 2): Standardized mean differences ranked 0.38 ([0.29; 0.46] $I^2$ 0%, $n = 7$) in maintenance studies, 0.21 ([0.17; 0.25] $I^2$ 11%, $n = 29$) in acute treatment studies, and 0.11 ([−0.05; 0.26] $I^2$ 51%, $n = 10$) in studies including patients with a primary physical condition plus major depression. Figure 2 provides a forest plot of all studies,

**TABLE 2** Measures of heterogeneity in random-effects meta-analyses based on RCTs reporting on antidepressant drug treatment effects on quality of life

| Outcome | # RCTs | Q (*p*-value) | $I^2$ | Point estimate, SMD | 95% confidence interval | 95% prediction interval |
|---|---|---|---|---|---|---|
| **QoL effect** | | | | | | |
| All studies | 46 | 73.5 (0.005) | 39% | 0.22 | 0.18–0.26 | 0.05–0.40 |
| Primary depression | 29 | 31.5 (0.29) | 11% | 0.21 | 0.18–0.25 | 0.14–0.29 |
| Secondary depression | 10 | 18.5 (0.029) | 51% | 0.11 | −0.05-0.26 | −0.33-0.55 |
| Maintenance | 7 | 2.7 (0.841) | 0% | 0.38 | 0.29–0.46 | n.a.[1] |

*Note*: Primary depression refers to RCTs on acute treatment of patients with major depressive disorder, secondary depression to RCTs on patients diagnosed with major depression comorbid to a primary somatic disorder. SMD, standardized mean difference.
[1]not applicable: In this subgroup meta-analysis, between-study variance, $tau^2$, equals 0, and the seven studies share a common effect size; therefore, no prediction interval can be computed. Positive SMD values indicate superiority of antidepressants.

and Table 2 summarizes heterogeneity measures of all main analyses, including prediction intervals.

Risk of bias analyses returned differences in summary SMDs in primary depression RCTs with only three trials carrying a low risk of bias: 0.18 [0.09; 0.27] vs. 0.22 [0.18; 0.26]. Among secondary depression trials seven had a low risk of bias, with a summary estimate of 0.01 [−0.13; 0.15] as opposed to an SMD of 0.44 [−0.01; 0.89] among the three uncertain/high RoB studies combined. We did not carry out a RoB analysis in maintenance RCTs because all carried a high risk of bias.

The majority of studies provided global QoL measures ($n = 30$), with a summary SMD of 0.21 ([0.16; 0.27] $I^2$ 45%). Sixteen studies reported mental health or depression related QoL, and the summary estimate amounted to 0.24 ([0.18; 0.30] $I^2$ 25%, $p = 0.50$ (Q, df 1)).

All but four studies were funded, partly or wholly, by drug manufacturers. Three of which examined antidepressants in secondary[21,41,46] and one in primary depression.[50] The latter yielded a positive effect on QoL – SMD: 0.24 [0.07; 0.41]. Across RCTs with patients diagnosed with depression secondary to a physical condition, the summary effect of seven industry-funded trials was 0.14 [−0.09; 0.38] versus 0.09 [−0.11; 0.28] among three industry-independent investigations ($p = 0.72$, df (Q): 1).

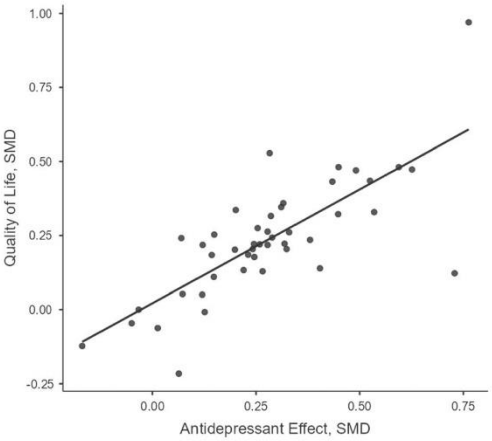


**FIGURE 3** Antidepressant and quality of life effects. (SMD denotes standardized mean difference. Spearman's correlation coefficient rho: 0.73 ($p < 0.001$), $N = 45$ double-blind, placebo-controlled randomized trials)

## 9 | SECONDARY OUTCOME

Forty-five studies provided results with regard to depression rating scales: The summary SMD between antidepressant and placebo arms was 0.27 ([0.22; 0.32] $I^2$ 48%). By indication, SMDs ranked 0.42 ([0.31; 0.53] $I^2$ 0%) in maintenance studies, 0.27 ([0.22; 0.32] $I^2$ 50%) in acute treatment studies of major depression, and 0.12 ([0.01; 0.23] $I^2$ 6%) among RCTs with secondary major depression ($p = 0.001$ (Q), df 2).

Quality of life efficacy and antidepressant efficacy of antidepressants at study level, both expressed as SMDs, were correlated, with a Spearman's rho of 0.73 ($p < 0.001$, Figure 3). This association also showed in meta-regression: slope: 0.46 [0.24–0.67], $p < 0.001$, df:1 (unrestricted maximum likelihood method), indicating that an increase of one SMD in antidepressant efficacy is accompanied by an increase of 0.46 SMD in quality of life.

The standardized mean differences of antidepressant pharmacotherapy regarding depression were statistically

significantly larger than SMDs regarding QoL, with a difference of 0.043 SMD [0.002; 0.085] (two-sided Wilcoxon rank test, W: 713, $p = 0.028$). This difference in effect sizes also has an effect size, owing to the nonparametric distribution of differences reported here as point-biserial correlation[68]: $r = 0.38$.

## 10 | DISCUSSION

In a large sample of placebo-controlled and double-blind RCTs we found a small effect of antidepressant pharmacotherapy on quality of life. The effect size decreased when we restricted computations to studies with low risk of bias: Only marginally so across acute treatment RCTs of major depressive disorder, but in studies on major depression secondary to somatic disorders the effect all but vanished. In maintenance treatment, notably, all seven studies carried a high risk of bias, and, as a consequence, we cannot estimate an effect size in low risk of bias studies. Thus, for maintenance treatment, we consider the certainty of the evidence as low.

We have divided our set of studies into three subgroups, defined by indication: acute treatment studies in primary major depression, studies on acute treatment of major depression among patients suffering from a somatic disorder (secondary depression), and maintenance treatment of patients with depression. Not only are the effects across these groups statistically significantly different, we also believe these indications are clinically so distinct it is more informative to view these groups seperately than to focus on a summary effect. In order to comply with our pre-registered research protocol, we present summary estimates of QoL and antidepressant effects across all studies, anyway, but we caution that these summary standardized mean differences refer to no actual population in psychiatry. By contrast, the three subgroups reflect different populations of patients we see in everyday clinical routine.

From the vantage point of clinical practice our finding of slightly better efficacy among primarily depressed than among secondarily depressed patients is plausible: Somatic disorders, such as kidney failure, diabetes, or heart failure may overshadow the positive effect on quality of life that could have been caused by antidepressants. On the other hand, the effect on QoL found in primary depression is small but seems robust after risk of bias analyses and without indication of small study effects, or publication bias, in this group. Still, the margins of the prediction interval (0.14 to 0.29, Table 2) mean that very small or stronger effects cannot be excluded.

It is difficult to interpret the relatively strong effect size measured across maintenance trials: Those RCTs carry a high risk of bias because all randomized participants in an enriched design in which responding patients – those that are in remission following acute treatment with an antidepressant – are allocated to placebo treatment or to continue the succesful antidepressant. While this design is pragmatic, withdrawal and rebound syndromes caused by discontinuation of antidepressants[69] in patients randomized to placebo arms can artificially increase recurrence rates or depression scale scores and thus inflate effect sizes in favor of antidepressants.[70 – 74] Among the studies included, Perahia et al. [20] and Kocsis et al.[47] explicitly mention this mechanism in their reports, although there were no attempts at quantification of withdrawal symptoms, for example, with the Discontinuation-Emergent Signs and Symtpoms Inventory (DESS).[75] At any rate, it is conceivable withdrawal effects also intrude upon the measurement of quality of life. As a result, the summary effect estimate for QoL in maintenance trials seems doubtful.

Relative to the improvement of quality of life caused by antidepressants their impact on depression was moderately, but statistically significantly larger, although with an SMD of 0.27 among acute treatment RCTs in primary depression the effect size is also considered small, at least within the conventions set by Cohen.[76] Still, an SMD of 0.27 fits well into summarizing literature of antidepressant effects.[13,16,77,78] For example, in a meta-analysis of antidepressant drug treatment at various time points between 8 and 24 weeks, effects remained within a range of 0.24 to 0.34.[14] Given the moderate effect size and absent clean-cut criteria of what constitutes a clinically meaningful improvement in quality of life, we argue that the case for a convincing effect is still out. That does not preclude important improvements in individual cases.

It is not surprising antidepressants were more effective with regard to their target syndrome than to quality of life. Although overall QoL, understood as general well-being, may be considered the more important outcome, it is hard to see how antidepressants should impact on all domains encompassed by QoL. In theory, psychotherapy, with its commonly more holistic approach, should be more successful in improving QoL. In fact, in a meta-anaylsis of 44 psychotherapy RCTs,[79] Kolovos and co-authors found a moderately stronger effect size with regard to QoL (SMD 0.33 [0.24–0.42]). And yet, the trials are difficult to compare, in part because many had wait-list control groups, not all included patients with major depressive disorder, and the more appropriate comparison to psychotherapy studies may be antidepressant maintenance RCTs. Adding to the difficulties in reconciling results from both treatment domains, patients in psychotherapy trials may differ from those in antidepressant drug treatment studies. Similar to our findings, however,

Kolovos et al.[79] reported stronger effects among patients with primary depression versus patients with comorbidity, and they also found better effects on depression than on QoL. Of note, among the 16 studies reporting depression-related or mental component quality of life measures in our meta-analyses, QoL results were only marginally higher than in the 30 studies employing global QoL measures (summary SMDs: 0.24 vs. 0.21) and still lower than antidepressant effects (summary SMD across 16 studies: 0.26).

A possible explanation for the difference between QoL related and antidepressant effects of antidepressants is that improvements in QoL may take longer than antidepressant effects[80] However, this theory is not supported by the observation that in the seven included maintenance trials – invariably starting after successful acute treatment and with a minimum duration of 6 months – the difference did not vanish (data not shown).

In our sample of studies, changes in quality of life scales were strongly correlated with changes in depression scores: With a correlation coefficient of 0.73 more than half of the variance in quality of life scores is accounted for by the variance in depression scores. In psychiatry and clinical psychology, a correlation of 0.73 is high by any standard. Even scales that measure the same latent variable, e.g., depression, show no perfect correlation. For example, Heo and co-authors found a correlation of 0.80 between baseline scores of HRDS-17 and MADRS[81] and when Hershenberg et al. correlated self-rating scales for depression, such as BDI, with the observer rated MADRS, r was below 0.7.[82]

The correlation cannot explain causality, that is, whether antidepressant effect improves quality of life or vice versa. However, the most likely reason for the association is overlap: QoL and depression scales share similar domains. In addition, mood may carry over in filling out rating scales in a more general way. In this sense, improved mood would lead to more positive ratings of items not necessarily related to mood, such as physical well-being. This hypothesis can be tested in more fine-grained item by item analyses but, unfortunately, not in the present material.

There are notable differences between QoL and depression instruments beyond their distinction as self- versus observer-rating scales: As an example, depression scales touch upon suicidality which is not an item in quality of life scales. Also, the observation time the instruments cover may differ. These differences may explain why the correlation we found is high but far from perfect and why almost half of the variance remains unexplained.

In line with the criticism voiced by De Fruyt and Demyttenaere more than a decade ago,[80] our results indicate that with the current practice future antidepressant RCTs will not gain much insight by including sum-scores of QoL instruments. In fact, in most papers reviewed here QoL results have mostly been reported only peripherally. Echoing another criticism by De Fruyt and Demyytenaere, choices of specific QoL scales have rarely been explained. In sum, the hope that assessing QoL in RCTs would widen the perspective beyond symptom reduction has not materialized yet.

For future RCTs it appears that subdomaines, such as physical health related quality of life provide additional information relative to mental health related QoL scores with their conceptual overlap with symptom scales. Also, it may be instructive to focus on social functioning. While not independent from depression, social functioning relates to important facets of personal life not covered by depression rating scales, such as one's ability to be gainfully employed or to fulfill one's domestic roles. However, it remains to be shown that social functioning is different fom QoL and can add new insights into antidepressant response measurement.

Several limitations of our study deserve notice: In combining a variety of quality of life scales we have introduced methodological variance. It is therefore reassuring that heterogeneity, measured as $I^2$ turned out to be at or below 50%. Of note, in the event that results of more than one QoL instrument were presented we followed a pre-registered decision rule for inclusion. Moreover, to consider more than one QoL instrument is not different from the approach to depression rating scales in the meta-analysis literature. While it would have been optimal all studies had employed the same QoL scale, this ideal seems to be unrealistic for the time being: In a literature review on QoL and dementia, Oppiköfer listed no less than 119 QoL tools.[83] This finding alludes to the fact that quality of life, while a useful concept, comes in several slightly different meanings. Again, this is similar to the situation with other scales used in psychiatry: The depression depicted in a HAM-D score is slightly different from the depression reflected in BDI or MADRS scores, to name only three instruments. It is good to know the effect sizes differed little in RCTs using global QoL instruments versus those with mental health related QoL measures.

We may have missed important studies. In antidepressant RCTs, QoL findings are not primary outcomes and may thus not appear in titles or abstracts. However, we followed established methods of detecting studies, and it is reassuring that we found no further QoL studies when we searched all reference lists of studies eventually included.

It also remains a possibility that negative QoL findings have not been reported in papers presenting antidepressant RCTs. Whereas it seems plausible QoL was reported only when effects were positive, we did not find

a signal of publication bias (small study effects) in various funnel plots and Egger tests. Among the effect sizes in regard to QoL, 59%, 27 out of 46, were statistically significantly different from unity – an indication that statistical significance may not have been the driving force in reporting QoL figures, and thus another argument against publication bias in this sample. In sum, so far, there is little to support a strong suspicion of publication bias in this field.

Further, all studies included in this meta-analysis were double-blind, but masking can be compromised, and only a small minority of trials measure, or report, the integrity of blinding.[84]

Every meta-analysis depends on the quality of the study pool, and we found a high or uncertain risk of bias in the majority of RCTs, including all seven maintenance trials. Moreover, risk of bias analyses resulted in marginally (primary depression) or considerably (secondary depression) lower effect sizes.

Initially, we planned to meta-analyze both quality of life and social functioning scales in one approach. However, while there is overlap and some of the scales used in the present meta-analysis on quality of life touch upon social functioning, we now believe they require specific analyses. Therefore, we will publish results on our meta-analyses of social functioning during antidepressant treatment in a later paper. Apart from the posthoc analyses documented and discussed above this is the main deviation from the protocol. As an aside, we registered the protocol as a free text following the structure of PROSPERO protocols because, at the time of registration, OSF did not offer a registration form for systematic reviews.

In conclusion, we have found a small effect of antidepressants on quality of life in primary depression that seems relatively robust whereas the effect found in patients suffering from depression comorbid to somatic disorders vanished in low risk of bias studies, and it remains unclear whether there is an effect at all in maintenance studies. The impact of antidepressants on depression seems to be slightly stronger than on QoL, and both measures are strongly correlated. The way QoL is currently assessed provides only limited information on the well-being of patients beyond symptomatic recovery.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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# 4. DISKUSSION

## 4.1 Beantwortung der Fragestellung

Das Ziel dieser Arbeit war herauszufinden, inwiefern eine Behandlung mit Antidepressiva die subjektive Lebensqualität verbessern kann. Die mit den unterschiedlichsten Messinstrumenten erhobenen QOL – Daten wurden mit Hilfe einer random-effects Metaanalyse zusammengeführt.

Laut Cohen ist eine Effektstärke (d) bis 0.2 als klein, 0.5 als mittel und 0.8 oder darüber als groß einzuschätzen[30]. Der Gesamteffekt aus den kombinierten 46 Studien von Antidepressiva vs. Placebo war 0.22 SMD [95%CI: 0.18; 0.26] klein, aber deutlich messbar.

In der Subgruppenanalyse war der Effekt in Studien mit hohen oder unklarem Risk of Bias größer (0.25 [0.20;0.29]) als in solchen die mit einem niedrigen Risk of Bias bewertet wurden (0.11 [0.01; 0.20]). Erhaltungsstudien (Maintenance Studies) zeigten mit 0.38 ([0.29; 0.46] I2 0%, n = 7) einen größeren Effekt als solche zur Akutbehandlung (Acute Treatment Studies) (0.21 ([0.17; 0.25] I2 11%, n = 29), wobei Studien mit Depression als Komorbidität einer somatischen Erkrankung fast keinen Effekt mehr aufwiesen (0.11 ([-0.05; 0.26] I2 51%, n = 10).

Nach Durchsicht der Ergebnisse lässt sich die anfangs gestellte Frage also folgendermaßen beantworten: Antidepressiva haben einen (wenn auch lt. Cohen kleinen[30]) Effekt auf die durch QOL-Fragebögen erhobene Lebensqualität von depressiven Patienten, wobei wie oben genannt unterschiedliche Effekte in der Subgruppenanalyse zu beachten sind.

## 4.2 Probleme der Arbeit

Mögliche Limitierungen des Projekts sind unter anderem die methodischen Schwächen der Metaanalyse. Dazu gehören zum Beispiel die Heterogenität, unterschiedliche Qualität („garbage in, garbage out“) und Aussagekraft der eingeschlossenen Studien. Es wird auch kritisch diskutiert, ob es sinnvoll ist eine solch heterogene Fülle an Information in einem, generalisierten Zahlenwert ausdrücken zu wollen[31].

Ein grundlegendes Problem der QOL-Forschung ist die Uneinheitlichkeit des Begriffs und der Mangel an klaren Kriterien zur Erhebung der Lebensqualität. Hinzu kommt die große Breite an verfügbaren Skalen - Oppikofer listet alleine 119 auf[32], die teilweise sehr unterschiedliche Aspekte von QOL abdecken. Obwohl wir uns bei Studien mit mehreren erfassten Skalen für die häufigeren entschieden und bei breit gefächerten Fragebögen wie dem SF-36[18] die

„Mental Component Score“ bevorzugten, führt dies zu einer methodischen Varianz, die schwer zu vernachlässigen ist.

Es ist auch schwierig, eine Verbesserung der Lebensqualität von einer reinen Symptomreduktion des depressiven Patienten durch die medikamentöse Therapie abzugrenzen, da wir in unserer Studie eine starke Korrelation zwischen Veränderung in QOL- und Depressions-Scores gefunden haben.

Obwohl wir in der Risk of Bias – Erhebung nur wenige Hinweise auf einen Publication Bias finden konnten, ist nicht auszuschließen, dass QOL-Ergebnisse nur mit positivem Effekt veröffentlich wurden - die meisten Studien wurden mit einem unklaren oder hohen Risk of Bias bewertet. Es ist anzumerken, dass der Effekt mit 0.25 in den Studien mit hohen oder unklaren Risk of Bias größer als bei solchen mit einem als niedrig eingestuften.

Es ist auch nicht auszuschließen, dass wir trotz sorgfältiger Recherche beim Screening von 1807 Suchresultaten Studien, die unsere Einschlusskriterien erfüllen würden, übersehen haben.

### 4.3 Schlussfolgerungen

Antidepressiva haben einen, wenn auch kleinen Effekt auf die in placebokontrollierten Studien erhobene, subjektive Lebensqualität. Dieser Effekt verändert sich in der Subgruppenanalyse: die Effektstärke nahm ab, wenn man nur die Studien mit low risk of bias betrachtete. In Studien zur primären Depression wurde der Effekt nicht kleiner, in Studien zur sekundären Depression als Komorbidität zu einer somatischen Erkrankung verschwand er fast. Alle Erhaltungsstudien wurden mit high risk of bias bewertet. Zwar ist deren berechneter Effekt größer als bei der primären Depression, aber da wir keine Erhaltungsstudien mit low risk of bias zur Verfügung hatten, können wir diesen nicht sicher beurteilen. Bei der primären Depression erscheinen die Ergebnisse dahin robust, ohne Hinweis auf risk of bias. Diese beiden Gruppen unterscheiden sich statistisch signifikant und bilden zusammen keine real in der Psychiatrie vorkommende Population ab, weshalb es Sinn macht, sie getrennt voneinander zu beurteilen. Um nicht vom Studienprotokoll abzuweichen, wurde der Gesamteffekt trotzdem berechnet, dieser ist aber aus oben genannten Gründen kritisch zu betrachten.

Der leicht größere Effekt von Antidepressiva bei primärer gegenüber sekundärer Depression erscheint klinisch plausibel, da somatische Erkrankungen wie Nierenversagen, Diabetes oder

Herzinsuffizienz deren positiven Effekte auf die Lebensqualität überlagern können. Im Maintenance-Arm der Studie dagegen könnten zum Beispiel Rebound-Effekte oder Entzugssymptome nach dem Absetzen der Antidepressiva in der Placebogruppe für das bessere Abschneiden der Wirkstoffgruppe herangezogen werden[33].

In 45 Studien konnten als sekundärer Endpunkt Daten aus Depressions-Skalen erhoben werden: die SMD von Antidepressiva vs. Placebo war 0.27 ([0.22; 0.32] $I^2$ 48%). Laut Cohen[30] ist der Effekt von Antidepressiva auf QOL zwar klein, auf Depression jedoch moderat und passt damit gut zu dem bereits in der Literatur beschriebenem Effekt[34-37]. In einer Metaanalyse von 2022 zur Behandlung mit Antidepressiva über Zeitspannen von 8 bis 24 Wochen finden sich zum Beispiel Effektstärken zwischen 0.24 und 0.34[38].

Es ist nicht überraschend, dass der Effekt von Antidepressiva auf ihr Zielsymptom der Depression größer ist als auf QOL. Außerdem ist es schwer vorstellbar, dass Antidepressiva Einfluss auf alle Komponenten dieses sehr umfangreichen Konzepts von allgemeinem Wohlbefinden haben könnten. Es wäre auch möglich, dass die Verbesserung von QOL länger dauert als die Reduktion von depressiven Symptomen[3].

In dieser Stichprobe von 46 Studien waren Veränderungen der QOL-Scores stark mit denen der Depressions-Scores korreliert: Mit einem Korrelationskoeffizienten (r) von 0,73 wird mehr als die Hälfte der Varianz in QOL-Scores durch die Varianz in den Depressions-Scores erklärt. In der Psychiatrie und klinischen Psychologie gilt eine Korrelation von 0,73 als hoch. Selbst Skalen, die dieselbe latente Variable messen, z.B. Depression, zeigen keine perfekte Korrelation. Zum Beispiel fanden Heo und Co-Autoren eine Korrelation von 0,80 zwischen den Ausgangswerten von HRDS-17 und MADRS[89] und als Hershenberg et al. die Selbstbewertungsskalen für Depression, wie BDI, mit der vom Untersucher erhobenen MADRS korrelierten, lag der Wert von r unter 0,7[39]. Die Korrelation zwischen antidepressiver Wirkung und Lebensqualität kann nicht die Kausalität erklären, daher ob die antidepressive Wirkung die Lebensqualität verbessert oder umgekehrt. Der wahrscheinlichste Grund für diese Assoziation ist der Überlappungsbereich zwischen den in QOL- und Depressions-Skalen abgefragten Domänen.

Es bestehen trotz vieler Überschneidungen auch erhebliche Unterschiede zwischen QOL- und Depressions-Messinstrumenten, die über die Unterscheidung zwischen Selbst- und Fremdbeurteilung hinausgehen. So berücksichtigen Depressions-Skalen beispielsweise die Suizidalität, die in QOL-Skalen kein Kriterium ist, weiters kann die Beobachtungszeit variieren.

Diese Unterschiede können zur Erklärung beitragen, warum die von uns gefundene Korrelation hoch, aber nicht perfekt ist und fast die Hälfte der Varianz unerklärt bleibt.

Kritik an der aktuellen Praxis der QOL-Messung in randomisierten Studien wurde bereits von mehreren Autoren[3,40] geäußert und umfasst die unklare Konzeptualisierung des zugrunde liegenden QOL-Konzepts, die unklare Definition spezifischer Messbereiche und die unklare Begründung dafür, warum ein bestimmtes Instrument verwendet wurde[3]. Tatsächlich wurden in den meisten hier überprüften Studien QOL-Ergebnisse nur am Rande berichtet und die Auswahl der eingesetzten QOL-Skalen in den wenigsten Fällen erklärt, sodass wir die geäußerte Kritik in dieser Studie bestätigt finden. Insgesamt lässt sich sagen, dass die Hoffnung, die Erfassung von QOL in RCTs würde die Perspektive über die reine Symptomreduktion hinaus erweitern, bisher nicht realisiert wurde.

Für zukünftige Studien könnte es sinnvoll sein, sich auf Subdomänen von QOL zu konzentrieren die Facetten des persönlichen Lebens abbilden, die nicht bereits durch Depressions-Scores oder die auf mentale Gesundheit bezogenen Aspekte von QOL-Skalen abgedeckt sind wie beispielsweise die soziale Funktion, welche wir parallel in einer anderen Studie untersucht haben[41].

Grundsätzlich ist die Entwicklung hin zur PRO und einer mehr patientenorientierten Forschung als positiv zu bewerten. Das Erheben von QOL als primärer oder sekundärer Endpunkt gibt der subjektiven Erfahrung des an Depression erkrankten Patienten einen größeren Stellenwert in der klinischen Forschung, welche sich oft primär auf Laborwerte oder durch den Untersucher erhobene Ergebnisse stützt. Nicht zuletzt liefern diese Daten auch wertvolle Erkenntnisse zu den bereits bekannten psychosozialen Auswirkungen der Erkrankung[4].

Zusammenfassend haben wir einen kleinen Effekt von Antidepressiva auf die Lebensqualität bei primärer Depression gefunden, der relativ robust erscheint, während der Effekt, der bei Patienten mit Depressionen in Kombination mit somatischen Erkrankungen gefunden wurde, in Studien mit geringem Risiko für Verzerrungen verschwand und es unklar bleibt, ob es überhaupt einen Effekt in Studien zur Erhaltungstherapie gibt. Der Einfluss von Antidepressiva auf die Depression scheint leicht stärker zu sein als auf die Lebensqualität, und beide Maße sind stark korreliert. Die Art und Weise, wie die Lebensqualität derzeit bewertet wird, liefert nur begrenzte Informationen über das allgemeine Wohlbefinden von depressiven Patienten über die symptomatische Genesung hinaus.

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# 6. ANHANG

## 6.1 Tabellen und Graphiken

### 6.1.1. Suchstrategie

Databases searched: Cochrane/CENTRAL, NLM databases, such as MEDLINE and PubMed Central via PubMed, PsycINFO

Search terms and their combination:

("antidepressant*" OR "agomelatin*" OR "amineptin*" OR "amitriptylin*" OR "amoxapin*" OR "bupropion*" OR "butriptylin*" OR "chlorimipramin*" OR "citalopram*" OR "clomipramin*" OR "desipramin*" OR "desvenlafaxin*" OR "dibenzepin*" OR "dosulepin*" OR "dothiepin*" OR "doxepin*" OR "duloxetin*" OR "escitalopram*" OR "fluoxetin*" OR "fluvoxamin*" OR "imipramin*" OR "isocarboxazid*" OR "levomilnacipran*" OR "lofepramin*" OR "maprotilin*" OR "mianserin*" OR "milnacipran*" OR "mirtazapin*" OR "moclobemid*" OR "nefazodon*" OR "nortriptylin*" OR "paroxetin*" OR "phenelzin*" OR "protriptylin*" OR "reboxetin*" OR "selegilin*" OR "sertralin*" OR "setiptilin*" OR "tianeptin*" OR "tranylcypromin*" OR "trazodon*" OR "trimipramin*" OR "venlafaxin*" OR "viloxazin*" OR "vortioxetin")

AND

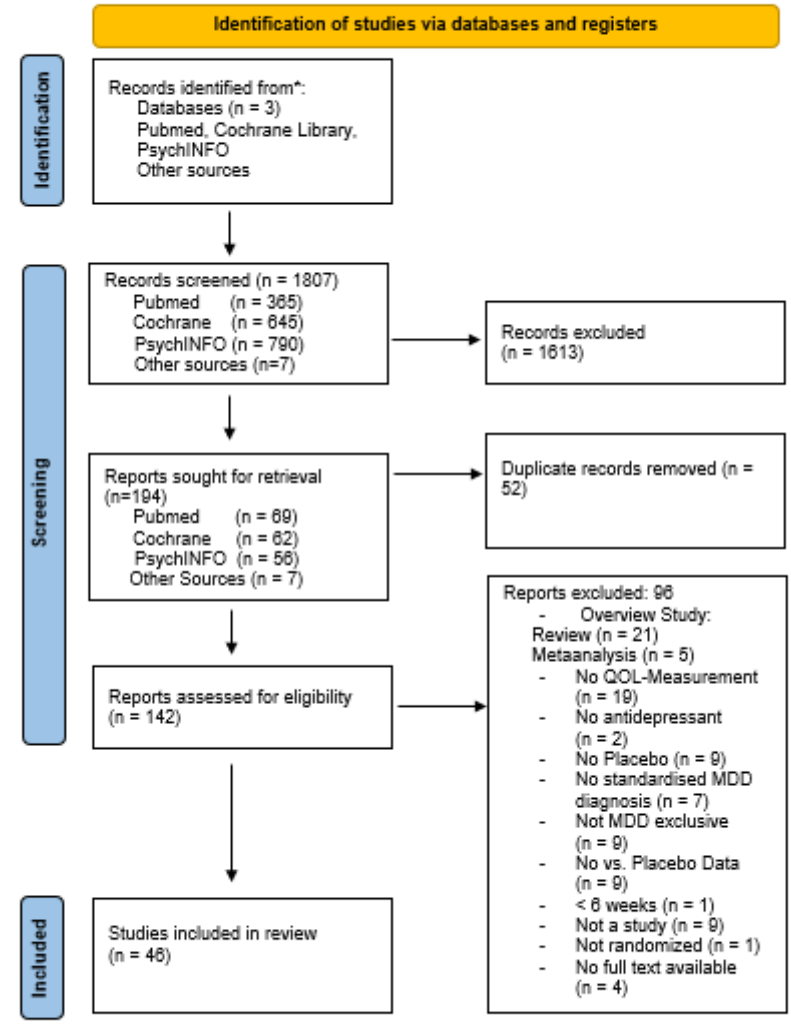
("placebo*" OR "PLC" OR "RCT" OR "randomiz*" OR "randomis*" OR "placebo*" OR "dummy*")

AND

("HRQOL" OR "QOL" OR "quality of life" OR "QOLS" OR "quality of life scale" OR "Quality of Life Enjoyment and Satisfaction Questionnaire" OR "Q-LES-Q" OR "SF-36" OR "SF-12" OR "Short-Form Health Survey" OR "WHO-QOL" OR "WHO-QOL 100" OR "Euroqol-5D-5L" OR "Euroqol-5D-3L" OR "EQ-5D" OR "EQ-5D-3L" OR "MANSA" OR "Manchester Short Assessment of Quality of Life" OR "Quality of life inventory" OR "QUOLI")

### 6.1.2. PRISMA Flowchart

**Figure 1. PRISMA Flowchart**




* no automation tools were used during screening

TABLE 1 (Continued)

| | Study | Year | Duration | acute/ maint. | n | Gender | Mean age | Comorbidity | Study drug | QOL | Severity of depression | Blinding of Participants | Risk of Bias |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 18 | **Gottlieb** | 2007 | 12 weeks | acute | 28 | f:14.3% m: 85.7% | 62 (10.58) | Chronic Heart Failure | Paroxetine 12–25 mg | SF-36, GH | BDI | Double blind | high |
| 19 | **Hedayati** | 2017 | 12 weeks | acute | 193 | f: 26.94% m: 73.06% | 58.4 (13.39) | Chronic Kidney Disease | Sertraline 50–200 mg | KDQOL-SF, GH | QIDS-C16 | Double blind | low |
| 20 | **Heiligenstein** | 1995 | 6 weeks | acute | 532 | f: 53.76% w: 46.24% | 67.65 (5.61) | Age 60+ | Fluoxetine 20 mg | SF-36 GH | HAM-D | Double blind | High |
| 21 | **Hewett 1** | 2009 | 8 weeks | acute | 543 | f: 79.33% m: 20.67 | 42.09 (11.56) | none | Bupropion 150–300 mg, Venlafaxine 75–150 mg | Q-LES-Q, LS | HAM-D MADRS CGI | Double blind | unclear |
| 22 | **Hewett 2** | 2010a | 10 weeks | acute | 418 | f: 72.01% m: 27.99% | 71.1 (5.75) | none | Bupropion 150–300 mg | Q-LES-Q, LS | HAM-D MADRS CGI | Double blind | unclear |
| 23 | **Hewett 3** | 2010b | 8 weeks | acute | 581 | f: 65.82% m: 34.18% | 44.75 (11.38) | none | Bupropion 150–300 mg, Venlafaxine 75–150 mg | Q-LES-Q, LS | HAM-D MADRS CGI | Double blind | unclear |
| 24 | **Kamijima** | 2006 | 16 weeks | acute | 235 | f: 63% m: 37% | 40 | none | Sertraline 50–100 mg | Q-LES-Q | HAM-D CGI | Double blind | high |
| 25 | **Kim** | 2014 | 24 weeks | m/c | 217 | (no info) | (no info) | ACS | Escitalopram 5–20 mg | WHQOL-BREF „social relationships" | BDI | Double blind | low |
| 26 | **Kocsis 1** | 2002 | 18 months | m/c | 161 | f: 66% m: 34% | 41.6 (9.4) | none | Sertraline 50–200 mg | SF-36 „role emotional" | HAM-D CGI | Double blind | high |
| 27 | **Kocsis 2** | 2007 | 52 weeks | m/c | 258 | f: 65% m: 35% | 42,3 | none | Venlafaxine ER (75–300 mg) | Q-LES-Q | HAM-D CGI | Double blind | high |
| 28 | **Kornstein** | 2010 | 8 weeks | acute | 372 | f: 100% | 52.34 (6.36) | none | Desvenlafaxine 50–100 mg | WHO-5 | HDRS, MADRS | Double blind | high |
| 29 | **Lewis** | 2019 | 12 weeks | acute | 527 | f: 59 & m: 41% | (no info) | none | Sertraline 50 mg | SF-12 MH | BDI-II CIS-R | Double blind | low |
| 30 | **Liebowitz 1** | 2007 | 8 weeks | acute | 234 | f: 60.26% m: 39.74 | 40.93 (12.71) | none | Desvenflaflaxine 100-200 mg | WHO-5 | HAM-D MADRS CGI | Double blind | unclear |
| 31 | **Liebowitz 2** | 2008 | 8 weeks | acute | 447 | f: 59.51% m: 40.49% | 42.66 (14.0) | none | Desvenlafaxine 50 mg, Desvenlaflaxine 100 mg | WHO-5 | HAM-D MADRS | Double blind | unclear |
| 32 | **Liebowitz 3** | 2013 | 8 weeks | acute | 673 | f: 60.77%, m: 39.23% | 41.99 (13.68) | none | Desvenflaflaxine 10 mg, Desvenlafaxine 50 mg | WHO-5 | HAM-D MADRS | Double blind | low |
| 33 | **Lydiard** | 1997 | 8 weeks | acute | 392 | f:30 66.58% m: 33.42% | 40.14 | none | Sertraline 50–200 mg, Amitryptiline 50–150 mg | Q-LES-Q, LS | HAM-D MADRS CGI | Double blind | unclear |

TABLE 1 (Continued)

| | Study | Year | Duration | acute/ maint. | n | Gender | Mean age | Comorbidity | Study drug | QOL | Severity of depression | Blinding of Participants | Risk of Bias |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 34 | **Perahia** | 2006 | 12 weeks | m/c | 269 | f: 72.66%<br>m: 27.34% | 45.24 (12.25) | none | Duloxetine 2x60 mg | QLSD | HAM-D<br>CGI-S | Double blind | high |
| 35 | **Phillipp** | 1999 | 8 weeks | acute | 151 | f: 75%<br>m: 25% | 47 (12) | none | Imipramine 100 mg | SF-36 MCS | HAM-D | Double blind | unclear |
| 36 | **Rapaport** | 2009 | 10 weeks | acute | 433 | f: 61,04%<br>m: 38.96% | 67.35 (6.49) | 60+ | Paroxetine 12,5 mg,<br>Paroxetine 25 mg | Q-LES-Q | HAM-D | Double blind | unclear |
| 37 | **Rouillon** | 2000 | 1 year | acute | 203 | f: 66.67%<br>m: 33.33% | 45 | none | Milnacipran 50 mg | DIP | HDRS<br>CGI | Double blind | high |
| 38 | **Schneider** | 2003 | 8 weeks | acute | 728 | f: 56.04%<br>m: 43.96% | 69.8 (6.65) | 60+ | Sertraline 50–100 mg | SF-36 GH | HAM-D<br>CGI | Double blind | unclear |
| 39 | **Stahl** | 2009 | 8 weeks | acute | 482 | f: 65.41%<br>m: 34.59% | 43.34 (12.29) | none | Agomeltain 25 mg,<br>Agomelstin 50 mg | QLDS | HAM-D<br>CGI | Double blind | unclear |
| 40 | **Swenson** | 2003 | 24 weeks | acute | 337 | f: 63.49%<br>m: 36.51% | 57.2 (10.75) | Post ACS | Sertraline 50–200 mg | Q-LES-Q | BDI | Double blind | unclear |
| 41 | **Thase** | 2016 | 8 weeks | acute | 372 | f: 65.5%<br>m: 34.5% | 44.75 (13.54) | none | Levomilnacipran 20-120 mg | SF-36 | MADRS | Double blind | unclear |
| 42 | **Trivedi** | 2004 | 8 weeks | acute | 387 | f: 58.37%<br>m: 41.63% | 38.8 (11.53) | none | Paroxetine 12,5 mg<br>Paroxetine 25 mg | Q-LES-Q | HAMD | Double blind | unclear |
| 43 | **Weintraub** | 2010 | 12 weeks | acute | 131 | f: 54%<br>m: 46% | 79 | Alzheimers Disease | Sertraline 50–100 mg | ADRQL | CSDD | Double blind | low |
| 44 | **Wise** | 2007 | 8 weeks | acute | 311 | no info | no info | Age 65+ | Duloxetine 60 mg | SF-36 MCS | HAM-D | Double blind | high |
| 45 | **Zajecka** | 2010 | 8 weeks | acute | 417 | f: 66.7%<br>m: 33.3% | 43.8 (12.22) | none | Agomelatine 25 mg,<br>Agomelatine 50 mg | QLDS | HAM-D | Double blind | unclear |
| 46 | **Zilcha-Mano** | 2013 | 16 weeks | acute | 105 | f: 59%<br>m: 41% | 37.5 (12.2) | none | Sertraline<br>Venlaflaxine | Q-LES-Q | BDI | Doubel blind | low |

### 6.1.4. Forrest Plot

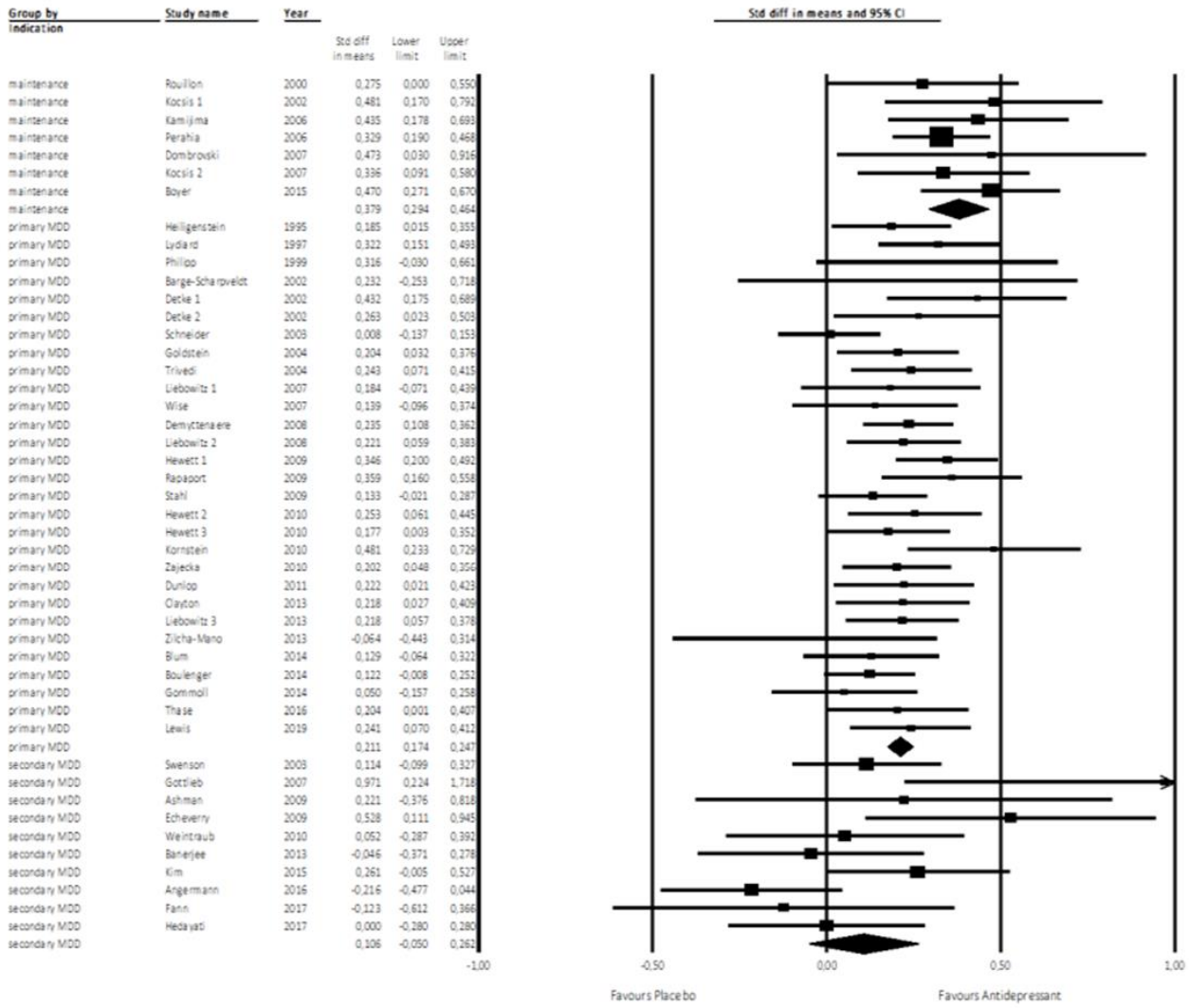


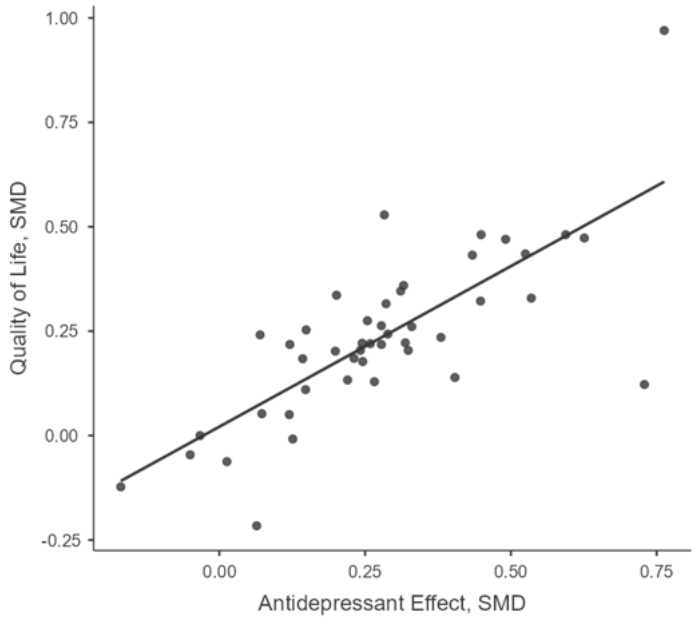

**Figure 2. Forest plot of Random-effects Meta-analyses of Maintenance Treatment and of Acute Treatment of Primary as well as Secondary Depression**

Legend: N=46 Double-blind, Placebo-controlled Randomized Trials, positive values indicate superiority of antidepressants.

## 6.1.5. Effekt von Antidepressiva auf QOL

**Fig 3. Antidepressant and quality of life effects.**

SMD denotes standardized mean difference. Spearman's correlation coefficient rho: 0.73 (p<0.001), N=45 double-blind, placebo-controlled randomized trials.




## 6.1.6. Maße der Heterogenität

TABLE 2 Measures of heterogeneity in random-effects meta-analyses based on RCTs reporting on antidepressant drug treatment effects on quality of life

| Outcome | # RCTs | Q (*p*-value) | $I^2$ | Point estimate, SMD | 95% confidence interval | 95% prediction interval |
|---|---|---|---|---|---|---|
| **QoL effect** | | | | | | |
| All studies | 46 | 73.5 (0.005) | 39% | 0.22 | 0.18–0.26 | 0.05–0.40 |
| Primary depression | 29 | 31.5 (0.29) | 11% | 0.21 | 0.18–0.25 | 0.14–0.29 |
| Secondary depression | 10 | 18.5 (0.029) | 51% | 0.11 | −0.05-0.26 | −0.33-0.55 |
| Maintenance | 7 | 2.7 (0.841) | 0% | 0.38 | 0.29–0.46 | n.a.[1] |

*Note*: Primary depression refers to RCTs on acute treatment of patients with major depressive disorder, secondary depression to RCTs on patients diagnosed with major depression comorbid to a primary somatic disorder. SMD, standardized mean difference.

[1]not applicable: In this subgroup meta-analysis, between-study variance, $tau^2$, equals 0, and the seven studies share a common effect size; therefore, no prediction interval can be computed. Positive SMD values indicate superiority of antidepressants.