Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2018-B-089 Esketamin

Stand: Juli 2018

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Esketamin
[Behandlung einer therapieresistenten Major Depression bei Erwachsenen]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe unter II.*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	• Psychotherapeutische Verfahren gemäß Psychotherapie-Richtlinie. • Elektrokonvulsionstherapie (EKT)
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	• Beschluss vom 16.09.2010 über eine Änderung der AM-RL: Anlage III – Übersicht der Verordnungseinschränkungen und -ausschlüsse – Reboxetin: Verordnungsausschluss • Beschluss vom 15.10.2015 über eine Änderung der AM-RL: Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Vortioxetin: Ein Zusatznutzen für Patienten mit leichten depressiven Episoden gegenüber beobachtendem Abwarten gilt als nicht belegt. Ein Zusatznutzen für Patienten mit mittelgradigen und schweren Episoden einer Major Depression gegenüber SSRI (mit dem Angebot einer psychotherapeutischen Behandlung bei schweren Episoden) ist nicht belegt.
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Esketamin	für die therapieresistente Depression (Major Depression bei Erwachsenen, die in der aktuellen mittelgradigen bis schweren depressiven Episode auf mindestens zwei unterschiedliche Behandlungen mit Antidepressiva nicht angesprochen haben) angewendet.
Im Therapiebereich Depression zugelassene Wirkstoffe :	
Sulpirid N05AL01 generisch	Depressive Erkrankungen, wenn die Behandlung mit einem anderen Antidepressivum erfolglos war.
Imipramin N06AA02 generisch	Depressive Syndrome unabhängig von ihrer nosologischen Einordnung.
Clomipramin, Clomipramin retard N06AA04 generisch	Depressive Syndrome unabhängig von ihrer nosologischen Zuordnung
Trimipramin N06AA06 generisch	Depressive Erkrankungen (Episoden einer Major Depression) mit den Leitsymptomen Schlafstörungen, Angst, innere Unruhe
Amitriptylin, Amitriptylin retard N06AA09 generisch	Depressive Erkrankungen.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Nortriptylin N06AA10 Nortrilen®	Depressive Zustandsbilder jeder Ätiologie, vor allem, wenn sie durch vitale Hemmung und Antriebsverarmung gekennzeichnet sind.
Doxepin N06AA12 generisch	Depressive Erkrankungen – Angstsyndrome – Leichte Entzugssyndrome bei Alkohol-, Arzneimittel- oder Drogenabhängigkeit – Unruhe, Angst oder Schlafstörungen im Zusammenhang mit depressiven Erkrankungen oder leichten Entzugssyndromen
Maprotilin N06AA21 generisch	Depressive Erkrankungen. Das Arzneimittel wird angewendet bei Erwachsenen
Amitriptylinoxid N06AA25 generisch	Behandlung depressiver Erkrankungen.
Fluoxetin N06AB03 generisch	Erwachsene: 1.1. Episoden einer Major Depression. 1.2. Zwangsstörung. 1.3. Bulimie: Fluoxetin ist als Ergänzung zu einer Psychotherapie angezeigt zur Reduktion von Essattacken und selbstinduziertem Erbrechen . 2. Kinder und Jugendliche, 8 Jahre alt und älter: Mittelgradige bis schwere Episoden einer Major Depression, wenn die Depression nach 4-6 Sitzungen nicht auf eine psychologische Behandlung anspricht. Hinweise zu den Anwendungsgebieten Ein antidepressives Arzneimittel sollte einem Kind oder jungen Menschen mit mittelgradiger bis schwerer Depression nur in Verbindung mit einer gleichzeitigen psychologischen Behandlung gegeben werden.
Citalopram N06AB04 generisch	Behandlung vom Episoden einer Major Depression.
Paroxetin N06AB05 generisch	Depressive Erkrankungen (Episoden einer Major Depression).
Sertralin N06AB07 generisch	Episoden einer Major Depression. Rezidivprophylaxe von Episoden einer Major Depression.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Fluvoxamin N06AB08 generisch	Depressive Erkrankungen (Episoden einer Major Depression).
Escitalopram N06AB10 generisch	Behandlung von Episoden einer Major Depression.
Tranylcypromin N06AF04 generisch	Zur Behandlung von depressiven Episoden (Episoden einer Major Depression). Hinweis: Das Arzneimittel sollte als Reserveantidepressivum zum Einsatz kommen, d.h. - wenn eine adäquate Therapie mit 2 antidepressiven Standardwirkstoffen (einschließlich trizyklische Antidepressiva) keinen ausreichenden Erfolg brachte oder - wenn solche Standardwirkstoffe kontraindiziert sind oder vom Patienten nicht vertragen werden.
Moclobemid N06AG02 generisch	Zur Behandlung von Episoden einer Major Depression. Hinweise zu den Anwendungsgebieten - Depressive Patienten, bei denen Erregung oder Agitiertheit die dominierenden klinischen Symptome darstellen, sollten entweder nicht mit Moclobemid behandelt werden oder es sollte für einen Zeitraum von max. 2 - 3 Wochen mit einem Sedativum kombiniert werden. - Patienten mit Schizophrenie oder schizoaffektiven Störungen sollten nur bei gleichzeitiger Gabe von neuroleptischen Arzneimitteln mit Moclobemid behandelt werden.
Mianserin N06AX03 generisch	Depressive Störungen.
Trazodon N06AX05 generisch	Depressive Erkrankungen, unabhängig von ihrer nosologischen Zuordnung.
Mirtazapin N06AX11 generisch	Behandlung depressiver Erkrankungen (Episoden einer Major Depression).
Bupropion N06AX12 generisch	Behandlung von Episoden einer depressiven Erkrankung (Episoden einer Major Depression).

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Tianeptin N06AX14 generisch	Zur Behandlung von Depressionen. Hinweise zu den Anwendungsgebieten Das Arzneimittel ist bei Erwachsenen indiziert.
Venlafaxin N06AX16 generisch	Behandlung von Episoden einer Major Depression. Rezidivprophylaxe von Episoden einer Major Depression.
Reboxetin N06AX18 Edronax®	Behandlung akuter depressiver Erkrankungen/Major Depression. Hinweise zu den Anwendungsgebieten Die Behandlung sollte bei Patienten, die initial auf Reboxetin angesprochen haben, zur Aufrechterhaltung der klinischen Besserung fortgeführt werden.
Duloxetin N06AX21 generisch	Zur Behandlung von depressiven Erkrankungen (Major Depression). Hinweise zu den Anwendungsgebieten Das Arzneimittel wird angewendet bei Erwachsenen.
Agomelatin N06AX22 Valdoxan®	Behandlung von Episoden einer Major Depression bei Erwachsenen.
Vortioxetin N06AX26 Brintellix®	Behandlung von Episoden einer Major Depression bei Erwachsenen.
Milnacipran N06AX17 Milnaneurax®	Behandlung von Episoden einer Major Depression bei Erwachsenen.
Johanniskraut N06AP01 Laif®	Pflanzliches Arzneimittel zur Behandlung von leichten bis mittelschweren depressiven Episoden.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Zulassung als Zusatztherapie:	
Quetiapin retard N05AH04 generisch	Quetiapin AbZ ist indiziert zur: • Behandlung der Schizophrenie. • Behandlung von bipolaren Störungen: ○ zur Behandlung von mäßigen bis schweren manischen Episoden bei bipolaren Störungen ○ zur Behandlung von schweren depressiven Episoden bei bipolaren Störungen ○ zur Rückfallprävention von manischen oder depressiven Episoden bei Patienten mit bipolaren Störungen, die zuvor auf eine Quetiapin-Behandlung angesprochen haben. • **Behandlung depressiver Erkrankungen (Episoden einer Major Depression) als Zusatztherapie bei Patienten, die unzureichend auf die Monotherapie mit einem Antidepressivum angesprochen haben** (siehe Abschnitt 5.1). Vor Beginn der Behandlung sollte der behandelnde Arzt das Sicherheitsprofil von Quetiapin beachten (siehe Abschnitt 4.4).
Zulassung für therapieresistente Depression:	
Quetiapin retard N05AH04 generisch	Quetiapin AbZ ist indiziert zur: • Behandlung der Schizophrenie. • Behandlung von bipolaren Störungen: ○ zur Behandlung von mäßigen bis schweren manischen Episoden bei bipolaren Störungen ○ zur Behandlung von schweren depressiven Episoden bei bipolaren Störungen ○ zur Rückfallprävention von manischen oder depressiven Episoden bei Patienten mit bipolaren Störungen, die zuvor auf eine Quetiapin-Behandlung angesprochen haben. • **Behandlung depressiver Erkrankungen (Episoden einer Major Depression) als Zusatztherapie bei Patienten, die unzureichend auf die Monotherapie mit einem Antidepressivum angesprochen haben** (siehe Abschnitt 5.1). Vor Beginn der Behandlung sollte der behandelnde Arzt das Sicherheitsprofil von Quetiapin beachten (siehe Abschnitt 4.4).
Lithiumcarbonat N05AN01 Hypnorex® retard	Bei bestimmten akuten Depressionen, z. B. bei Therapieresistenz oder Unverträglichkeit von Antidepressiva.

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2018-B-089 Esketamin

Auftrag von: Abt. AM

bearbeitet von: Abt. FB Med

Datum: 18.01.2018

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation *Major Depression* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 14.12.2017 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 1848 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 38 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

Zur Behandlung von Episoden einer Major Depression bei erwachsenen Patienten, die unzureichend auf mindestens eine vorherige Therapie mit Antidepressiva angesprochen oder diese nicht vertragen haben.

Abkürzungen:

AD	Antidepressiva
AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BD	bipolar disorder
CBT	Cognitive Behavioral Therapy
CGI–I	Clinical Global Impression–Improvement scale
CGI–S	Clinical Global Impression–Severity scale
DAHTA	DAHTA-Datenbank
ECT	Electroconvulsive
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
HAM-D	Hamilton Rating Scale for Depression
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
MADRS	Montgomery Asberg Depression Rating Scale
MAOI	Monoamine oxidase inhibitors
MDD	Major depressive disorder
n.s.	Nicht signifikant
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
PDD	Persistent Depressive Disorder:
RCT	Randomized controlled trial
RD	Risk difference
rTMS	repetitive transcranial magnetic stimulation
SARI	Serotonin antagonist and reuptake inhibitor
SDS	Sheehan Disability Scale
SIGN	Scottish Intercollegiate Guidelines Network
SNRI	Serotonin-norepinephrine reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitors
TCA	Tricyclics
TRD	Treatment-resistant depression
TRIP	Turn Research into Practice Database
WHO	World Health Organization

G-BA Beschlüsse/IQWiG Berichte

G-BA, 2015 [8]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Vortioxetin	**Zugelassenes Anwendungsgebiet:** Vortioxetin (Brintellix®) wird angewendet zur Behandlung von Episoden einer Major Depression bei Erwachsenen. a) Leichte Episode einer Major Depression **Zweckmäßige Vergleichstherapie:** Beobachtendes Abwarten (zur Behandlung leichter depressiver Episoden ist in der Regel keine Arzneimitteltherapie erforderlich). **Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Vortioxetin bei leichten Episoden einer Major Depression gegenüber der zweckmäßigen Vergleichstherapie:** Ein Zusatznutzen gilt als nicht belegt. b) Mittelgradige Episode einer Major Depression **Zweckmäßige Vergleichstherapie:** Die Arzneimitteltherapie erfolgt, sofern indiziert, mit einem Antidepressivum aus der Wirkstoffgruppe der selektiven Serotonin-Wiederaufnahmehemmer (SSRI). **Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Vortioxetin bei mittelgradigen Episoden einer Major Depression gegenüber der zweckmäßigen Vergleichstherapie:** Ein Zusatznutzen ist nicht belegt. c) Schwere Episode einer Major Depression **Zweckmäßige Vergleichstherapie:** Die Arzneimitteltherapie erfolgt, sofern indiziert, mit einem Antidepressivum aus der Wirkstoffgruppe der selektiven Serotonin-Wiederaufnahmehemmer (SSRI). Eine psychotherapeutische Behandlung soll angeboten werden. **Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Vortioxetin bei schweren Episoden einer Major Depression gegenüber der zweckmäßigen Vergleichstherapie:** Ein Zusatznutzen ist nicht belegt.
G-BA, 2010 [7]. Bekanntmachung eines Beschlusses des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage III – Übersicht der Verordnungseinschränkungen und –ausschlüsse: Reboxetin	Der Gemeinsame Bundesausschuss hat in seiner Sitzung am 16. September 2010 beschlossen, die Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (Arzneimittel-Richtlinie) in der Fassung vom 18. Dezember 2008/ 22. Januar 2009 (BAnz. Nr. 49a vom 31. März 2009), zuletzt geändert am 21. Oktober 2010 (BAnz. S. 3925), wie folgt zu ändern: Die Anlage III wird um eine Nummer 51 ergänzt: Reboxetin: Verordnungsausschluss verschreibungspflichtiger Arzneimittel nach dieser Richtlinie.

Cochrane Reviews

Guaiana G et al., 2013 [9]. Agomelatine versus other antidepressive agents for major depression	1. Fragestellung 1) to determine the efficacy of agomelatine in alleviating acute symptoms of major depressive disorder in comparison with other antidepressants, 2) to review the acceptability of agomelatine in comparison with other antidepressant drugs, 3) to investigate the adverse effects of agomelatine, including the general prevalence of side effects in adults.
	2. Methodik Population: Participants of both sexes, aged 18 years or older, with a primary diagnosis of major depression. Intervention: Agomelatine Komparatoren: Selective serotonin reuptake inhibitors (SSRIs; fluoxetine, fluvoxamine, citalopram, paroxetine, escitalopram); Serotonin-norepinephrine reuptake inhibitors (SNRIs; venlafaxine, duloxetine, milnacipran); Other antidepressive agents (tricyclic or heterocyclic antidepressants; monoamine oxidase inhibitors (MAOIs); newer agents (mirtazapine, bupropion, reboxetine); atypical antipsychotics in monotherapy (risperidone, paliperidone, olanzapine, quetiapine, aripiprazole, amisulpride, ziprasidone); non-conventional (herbal products such as Hypericum). Endpunkte: • Primärer Endpunkt: the number of participants who responded to treatment, showing a reduction of at least 50% on the Hamilton Rating Scale for Depression (HAM-D), the Montgomery Asberg Depression Rating Scale (MADRS), or any other depression scale (e.g. the Beck Depression Inventory, or the CES-D scale; or were 'much or very much improved' (score 1 or 2) on the Clinical Global Impression-Improvement (CGI-I) • Sekundäre Endpunkte: Remission, drop-out rate, side effects Recherche: Cochrane Collaboration's Depression, Anxiety and Neurosis Review Group's Specialised Register (CCDANCTR) to 31 July 2013. Anzahl eingeschlossene Studien/Patienten (Gesamt): A total of 13 studies (4495 participants) were included in this review Qualitätsbewertung der Studien: Cochrane risk of bias /GRADE
	3. Ergebnisdarstellung <u>Qualität der Studien</u>: With regard to the quality of the body of evidence, there was a moderate risk of bias for all outcomes, due to the number of included unpublished studies. There was some heterogeneity,

	particularly between published and unpublished studies. The included studies were conducted in inpatient and outpatient settings, thus limiting the generalisability of the results to primary care settings. Publication bias was variable and depended on the outcome of the trial. Our review included unpublished studies, and we think that this reduced the impact of publication bias. The overall methodological quality of the studies was not very good. Almost all of the studies were sponsored by the pharmaceutical company that manufactures agomelatine (Servier), and some of these were unpublished. Attempts to contact the pharmaceutical company Servier for additional information on all unpublished studies were unsuccessful. • Agomelatine was compared to selective serotonin reuptake inhibitors (SSRIs), namely paroxetine, fluoxetine, sertraline, escitalopram, and to the serotonin-norepinephrine reuptake inhibitor (SNRI), venlafaxine. Participants were followed up for six to 12 weeks. • Agomelatine did not show any advantage or disadvantage over the other antidepressants for our primary outcome, response to treatment • Also, agomelatine showed no advantage or disadvantage over other antidepressants for remission compared to SSRIs • Overall, agomelatine appeared to be better tolerated than venlafaxine in terms of lower rates of drop outs (RR 0.40; 95% CI 0.24 to 0.67, P value 0.0005), and showed the same level of tolerability as SSRIs (• Agomelatine induced a lower rate of dizziness than venlafaxine (RR 0.19, 95% CI 0.06 to 0.64, P value 0.007).
	4. Fazit der Autoren: Agomelatine did not seem to provide a significant advantage in efficacy over other antidepressive agents for the acute-phase treatment of major depression. Agomelatine was better tolerated than paroxetine and venlafaxine in terms of overall side effects, and fewer participants treated with agomelatine dropped out of the trials due to side effects compared to sertraline and venlafaxine, but data were limited because the number of included studies was small. We found evidence that compared agomelatine with only a small number of other active antidepressive agents, and there were only a few trials for each comparison, which limits the generalisability of the results. Moreover, the overall methodological quality of the studies was low, and, therefore, no firm conclusions can be drawn concerning the efficacy and tolerability of agomelatine. 5. Kommentare zum Review • keine Angaben oder separate Analysen zur Vortherapie
Koesters M et	1. Fragestellung

al., 2017 [17]. Vortioxetine for depression in adults Siehe auch: **Meeker AS et al. 2015 [25]**	To assess the efficacy and acceptability of Vortioxetine compared with placebo and other antidepressant drugs in the treatment of acute depression in adults.
	2. Methodik Population: Participants with a primary diagnosis of unipolar major depression according to DSM-III. Participants of both sexes, of any ethnicity, and aged 18 years and older Intervention: Vortioxetine monotherapy Komparator: Placebo; Another antidepressant as monotherapy, including: conventional TCA or heterocyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, dosulepin/dothiepin, doxepin, imipramine, lofepramine, maprotiline, nortriptyline, protriptyline, trimipramine); SSRIs (fluoxetine, fluvoxamine, citalopram, paroxetine, escitalopram); SNRIs (venlafaxine, duloxetine, milnacipran); MAOIs (phenelzine, isocarboxazide, tranylcypromine, moclobemide, brofaromine); other antidepressant agents (mirtazapine, bupropion, reboxetine, agomelatine) or non-conventional antidepressive agents (herbal products such as hypericum) Endpunkte: Response to treatment (primärer Endpunkt); Remission, Symptome, drop-out rate, side effects Recherche: Cochrane's Depression, Anxiety and Neurosis Review Group's Specialised Register to May 2016 Anzahl eingeschlossene Studien/Patienten (Gesamt): We included 15 studies (7746 participants) in this review. Seven studies were placebo controlled; eight studies compared vortioxetine to serotonin-norepinephrine reuptake inhibitors (SNRIs). No studies that compared vortioxetine to antidepressant drugs from other classes, such as selective serotonin reuptake inhibitors (SSRIs) were found. Qualitätsbewertung der Studien: Cochrane risk of bias / GRADE
	3. Ergebnisdarstellung <u>Qualität der Studien</u>: We judged none of the studies to have a high risk of bias for any domain, but we rated all studies to have an unclear risk of bias of selective reporting and other biases. • Vortioxetine may be more effective than placebo across the three efficacy outcomes: response (RR 1.35, 95% CI 1.22 to 1.49; 14 studies, 6220 participants), remission (RR 1.32, 95% CI 1.15 to 1.53; 14 studies, 6220 participants) and depressive symptoms measured using the Montgomery-Åsberg Depression Scale (MADRS) (score range: 0 to 34; higher score means worse outcome: MD -2.94, 95%

	CI -4.07 to -1.80; 14 studies, 5566 participants) →The quality of the evidence was low for response and remission and very low for depressive symptoms. • We found no evidence of a difference in total dropout rates. • More participants discontinued vortioxetine than placebo because of adverse effects (RR 1.41, 95% CI 1.09 to 1.81; 14 studies, 6220 participants) but fewer discontinued due to inefficacy (RR 0.56, 95% CI 0.34 to 0.90, P = 0.02; 14 studies, 6220 participants). → The quality of the evidence for dropouts was moderate. The subgroup and sensitivity analyses did not reveal factors that significantly influenced the results. • In comparison with other antidepressants, very low-quality evidence from eight studies showed no clinically significant difference between vortioxetine and SNRIs as a class for response. There was a small difference favouring SNRIs for depressive symptom scores on the MADRS (n.s.). • Very low quality evidence from eight studies (3159 participants) showed no significant differences between vortioxetine and the SNRIs as a class for total dropout rates, dropouts due to adverse events and dropouts due to inefficacy. • Against individual antidepressants, analyses suggested that vortioxetin may be less effective than duloxetine in terms of response rates (RR 0.86, 95% CI 0.79 to 0.94; 6 studies, 2392 participants) and depressive symptoms scores on the MADRS scale (MD 1.99, 95% CI 1.15 to 2.83; 6 studies; 2106 participants). • Against venlafaxine, meta-analysis of two studies found no statistically significant differences. • In terms of number of participants reporting at least one adverse effect (tolerability), Vortioxetine was better than the SNRIs as a class (RR 0.90, 95% CI 0.86 to 0.94; 8 studies, 3134 participants) and duloxetine (RR 0.89, 95% CI 0.84 to 0.95; 6 studies; 2376 participants). However, the sensitivity analysis casts some doubts on this result, as only two studies used comparable dosing.
	4. Fazit der Autoren: The place of vortioxetine in the treatment of acute depression is unclear. Our analyses showed vortioxetine may be more effective than placebo in terms of response, remission and depressive symptoms, but the clinical relevance of these effects is uncertain. Furthermore, the quality of evidence to support these findings was generally low. In comparison to SNRIs, we found no advantage for vortioxetine. Vortioxetine was less effective than duloxetine, but fewer people reported adverse effects when treated with vortioxetine compared to duloxetine. However, these findings are uncertain and not well supported by evidence. A major limitation of the current evidence is the lack of comparisons with the SSRIs, which are usually recommended as first-line treatments for acute

	depression. Studies with direct comparisons to SSRIs are needed to address this gap and may be supplemented by network meta-analyses to define the role of vortioxetine in the treatment of depression. 5. Kommentare zum Review • keine Angaben oder separate Analysen zur Vortherapie
Magni LR et al., 2013 [21]. Fluoxetine versus other types of pharmacotherapy for depression	1. Fragestellung To assess the effects of fluoxetine in comparison with all other antidepressive agents for depression in adult individuals with unipolar major depressive disorder.
	2. Methodik Population: The review included participants 18 years or older, of both sexes, with a primary diagnosis of unipolar major depression Intervention/Komparator: Experimental intervention: Fluoxetine (as monotherapy). Comparator interventions • Conventional antidepressive agents: tricyclics (TCAs); heterocyclics; SSRIs; SNRIs; MAOIs or newer ADs; and other conventional psychotropic drugs. • Non-conventional antidepressive agents: hypericum; and other non-conventional antidepressive agents (e.g. Crocus sativus). Endpunkte: Number of participants who responded to treatment (primärer Endpunkt); failure to complete due to any reason, Failure to complete due to inefficacy; failure to complete due to side effects Recherche: We searched the Cochrane Collaboration Depression, Anxiety and Neurosis Review Group Controlled Trials Register (CCDANCTR) to 11 May 2012 Anzahl eingeschlossene Studien/Patienten (Gesamt): A total of 171 studies were included in the analysis (24,868 participants). The included studies were undertaken between 1984 and 2012. Qualitätsbewertung der Studien: Cochrane risk of bias / GRADE
	3. Ergebnisdarstellung <u>Qualität der Studien</u>: The assessment of quality with the risk of bias tool revealed that the great majority of them failed to report methodological details, like the method of random sequence generation, the allocation concealment and blinding. Moreover, most of the included studies were sponsored by drug companies, so the potential for overestimation of

	treatment effect due to sponsorship bias should be considered in interpreting the results. • Fluoxetine was as effective as the TCAs when considered as a group both on a dichotomous outcome (reduction of at least 50% on the Hamilton Depression Scale) and a continuous outcome. • On a dichotomous outcome, fluoxetine was less effective than dothiepin or dosulepin (OR 2.13, 95% CI 1.08 to 4.20; number needed to treat (NNT) = 6, 95% CI 3 to 50, 2 RCTs, 144 participants), sertraline (OR 1.37, 95% CI 1.08 to 1.74; NNT = 13, 95% CI 7 to 58, 6 RCTs, 1188 participants), mirtazapine (OR 1.46, 95% CI 1.04 to 2.04; NNT = 12, 95% CI 6 to 134, 4 RCTs, 600 participants) and venlafaxine (OR 1.29, 95% CI 1.10 to 1.51; NNT = 11, 95% CI 8 to 16, 12 RCTs, 3387 participants). • On a continuous outcome, fluoxetine was more effective than ABT-200 (SMD -1.85, 95% CI -2.25 to -1.45, 1 RCT, 141 participants) and milnacipran (SMD -0.36, 95% CI -0.63 to -0.08, 2 RCTs, 213 participants); conversely, it was less effective than venlafaxine (SMD 0.10, 95% CI 0 to 0.19, 13 RCTs, 3097 participants). • Fluoxetine was better tolerated than TCAs considered as a group (total dropout OR 0.79, 95% CI 0.65 to 0.96; NNT = 20, 95% CI 13 to 48, 49 RCTs, 4194 participants) and was better tolerated in comparison with individual ADs, in particular amitriptyline (total dropout OR 0.62, 95% CI 0.46 to 0.85; NNT = 13, 95% CI 8 to 39, 18 RCTs, 1089 participants), and among the newer ADs ABT-200 (total dropout OR 0.18, 95% CI 0.08 to 0.39; NNT = 3, 95% CI 2 to 5, 1 RCT, 144 participants), pramipexole (total dropout OR 0.12, 95% CI 0.03 to 0.42, NNT = 3, 95% CI 2 to 5, 1 RCT, 105 participants), and reboxetine (total dropout OR 0.60, 95% CI 0.44 to 0.82, NNT = 9, 95% CI 6 to 24, 4 RCTs, 764 participants).
	4. Fazit der Autoren: The present study detected differences in terms of efficacy and tolerability between fluoxetine and certain ADs, but the clinical meaning of these differences is uncertain. Moreover, the assessment of quality with the risk of bias tool showed that the great majority of included studies failed to report details on methodological procedures. Of consequence, no definitive implications can be drawn from the studies' results. The better efficacy profile of sertraline and venlafaxine (and possibly other ADs) over fluoxetine may be clinically meaningful, as already suggested by other systematic reviews. In addition to efficacy data, treatment decisions should also be based on considerations of drug toxicity, patient acceptability and cost. 5. Kommentare zum Review: • keine Angaben oder separate Analysen zur Vortherapie
Purgato M et al.,	1. Fragestellung

2014 [31]. Paroxetine versus other anti-depressive agents for depression	1. To determine the efficacy of paroxetine in comparison with other anti-depressive agents in alleviating the acute symptoms of Major Depressive Disorder. 2. To review acceptability of treatment with paroxetine in comparison with other anti-depressive agents. 3. To investigate the adverse effects of paroxetine in comparison with other anti-depressive agents.
	2. Methodik Population: The review included participants 18 years or older, of both sexes, with a primary diagnosis of unipolar major depression Intervention: Paroxetine Komparator: Conventional anti-depressive agents 1. Older ADs: Tricyclics; Heterocyclics; MAOIs. 2. SSRIs 3.Newer or non-conventional anti-depressive agents, for example: SNRIs; Hypericum Endpunkte: Response rate (primärer Endpunkt), remission rate and continuous outcomes, acceptability, tolerability Recherche: The Cochrane Depression, Anxiety and Neurosis Review Group's Specialized Register (CCDANCTR, to 30 September 2012), which includes relevant randomised controlled trials from the following bibliographic databases: The Cochrane Library (all years), EMBASE (1974 to date), MEDLINE (1950 to date) and PsycINFO (1967 to date). Anzahl eingeschlossene Studien/Patienten (Gesamt): A total of 115 randomised controlled trials (26,134 participants) were included. In 54 studies paroxetine was compared with older ADs, in 21 studies with another SSRI, and in 40 studies with a newer or non-conventional antidepressant other than SSRIs. Qualitätsbewertung der Studien: Cochrane risk of bias / GRADE
	3. Ergebnisdarstellung <u>Qualität der Studien</u>: Included studies were generally at unclear or high risk of bias due to poor reporting of allocation concealment and blinding of outcome assessment, and incomplete reporting of outcomes. → Siehe auch Angaben bei den Ergebnissen! • For the primary outcome (patients who responded to treatment), paroxetine was more effective than reboxetine at increasing patients who responded early to treatment (Odds Ratio (OR): 0.66, 95% Confidence Interval (CI) 0.50 to 0.87, number needed to treat

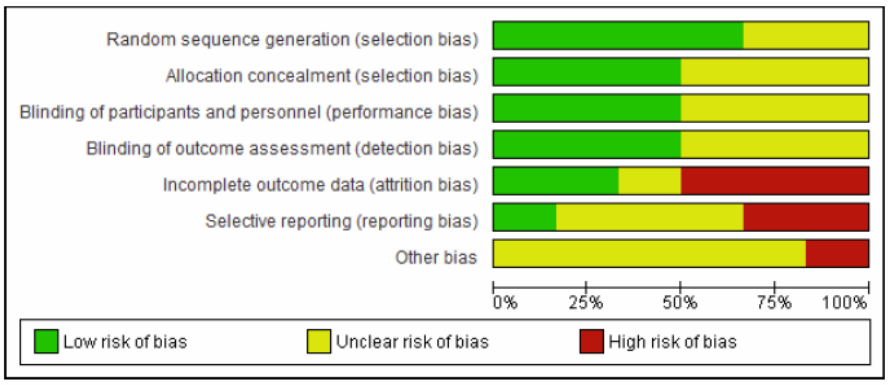
	to provide benefit (NNTb) = 16, 95% CI 10 to 50, at one to four weeks, 3 RCTs, 1375 participants, moderate quality of evidence), and less effective than mirtazapine (OR: 2.39, 95% CI 1.42 to 4.02, NNTb = 8, 95% CI 5 to 14, at one to four weeks, 3 RCTs, 726 participants, moderate quality of evidence). • Paroxetine was less effective than citalopram in improving response to treatment (OR: 1.54, 95% CI 1.04 to 2.28, NNT = 9, 95% CI 5 to 102, at six to 12 weeks, 1 RCT, 406 participants, moderate quality of evidence). • We found no clear evidence that paroxetine was more or less effective compared with other antidepressants at increasing response to treatment at acute (six to 12 weeks), early (one to four weeks), or longer term follow-up (four to six months). Paroxetine was associated with a lower rate of adverse events than amitriptyline, imipramine and older ADs as a class, but was less well tolerated than agomelatine and hypericum.
	4. Fazit der Autoren: Some possibly clinically meaningful differences between paroxetine and other ADs exist, but no definitive conclusions can be drawn from these findings. In terms of response, there was a moderate quality of evidence that citalopram was better than paroxetine in the acute phase (six to 12 weeks), although only one study contributed data. In terms of early response to treatment (one to four weeks) there was moderate quality of evidence that mirtazapine was better than paroxetine and that paroxetine was better than reboxetine. However there was no clear evidence that paroxetine was better or worse compared with other antidepressants at increasing responseto treatment at any time point. Even if some differences were identified, the findings from this review are better thought as hypothesisforming rather than hypothesis testing and it would be reassuring to see the conclusions replicated in future trials. Finally, most ofincluded studies were at unclear or high risk of bias, and were sponsored by the drug industry. The potential for overestimation oftreatment effect due to sponsorship bias should be borne in mind. 5. Kommentare zum Review: keine Angaben oder separate Analysen zur Vortherapie
Shinohara K et al., 2013 [32]. Behavioural therapies versus other psychological	1. Fragestellung 1. To examine the effects of all BT approaches compared with all other psychological therapy approaches for acute depression. 2. To examine the effects of different BT approaches (behavioural therapy, behavioural activation, social skills training and relaxation training) compared with all other psychological therapy approaches for

therapies for depression	acute depression. 3. To examine the effects of all BT approaches compared with different psychological therapy approaches (CBT, third wave CBT, psychodynamic, humanistic and integrative psychological therapies) for acute depression.
	2. Methodik Population: Studies of men and women aged ≥ 18 years were included Intervention: BT approaches eligible for inclusion were grouped into four main subcategories, according to the specific therapeutic principles and techniques described by trial authors, as follows: behavioural therapy (based on the Lewinsohn model, which focuses on increasing pleasant activities), behavioural activation (originated from the behavioural component of cognitive-behavioural therapy), social skills training/assertiveness training and relaxation therapy Komparator: The comparator intervention consisted of all other types of psychological therapies, categorised as CBT, third wave CBT, psychodynamic, humanistic and integrative approaches Endpunkte: Treatment response (primärer Endpunkt), number of participants who remitted while receiving treatment, Improvement in depression symptoms, Improvement in overall symptoms, Improvement in anxiety symptoms, Adverse effects, Social adjustment and social functioning, Quality of life Recherche: The Cochrane Depression Anxiety and Neurosis Group Trials Specialised Register (CCDANCTR, 31/07/2013), which includes relevant randomised controlled trials from The Cochrane Library (all years), EMBASE, (1974-), MEDLINE (1950-) and PsycINFO (1967-). Anzahl eingeschlossene Studien/Patienten (Gesamt): Twenty-five trials involving 955 participants compared behavioural therapies with one or more of five other major categories of psychological therapies (cognitive-behavioural, thirdwave cognitive-behavioural, psychodynamic, humanistic and integrative therapies). Qualitätsbewertung der Studien: Cochrane risk of bias / GRADE
	3. Ergebnisdarstellung <u>Qualität der Studien</u>: Most studies had a small sample size and were assessed as being at unclear or high risk of bias. • Compared with all other psychological therapies together, behavioural therapies showed no significant difference in response

	rate or in acceptability. • Similarly, in comparison with each of the other classes of psychological therapies, low-quality evidence showed better response to cognitive-behavioural therapies than to behavioural therapies (n.s.) and low-quality evidence of better response to behavioural therapies over psychodynamic therapies (n.s.). • When compared with integrative therapies and humanistic therapies, only one study was included in each comparison, and the analysis showed no significant difference between behavioural therapies and integrative or humanistic therapies. Subgruppenanalyse ,,Excluding studies in which the number of sessions was greater than 12'' : Because the number of studies was insufficient, we conducted sensitivity analyses that excluded studies in which the number of sessions was greater than 12. The results did not change the main findings of primary outcomes
	4. Fazit der Autoren: We found low- to moderate-quality evidence that behavioural therapies and other psychological therapies are equally effective. The current evidence base that evaluates the relative benefits and harms of behavioural therapies is very weak. This limits our confidence in both the size of the effect and its precision for our key outcomes related to response and withdrawal. Studies recruiting larger samples with improved reporting of design and fidelity to treatment would improve the quality of evidence in this review.

Systematische Reviews

Kishi T et al., 2017 [16]. A Meta-Analysis of Memantine for Depression	1. Fragestellung An updated meta-analysis of memantine for the treatment of depressive symptoms by combining data from MDD trials and BD trials.
	2. Methodik Population: MDD and BD patients Intervention: Memantine Komparator: Placebo Endpunkte: response rate (primärer Endpunkt), rate, improvement in depressive symptoms scale score, discontinuation due to inefficacy, all-cause discontinuation, discontinuation due to adverse events, and the individual adverse effects Recherche: systematische Literaturrecherche bis 2016

	Anzahl eingeschlossene Studien/Patienten (Gesamt): In total, six trials including 451 patients were identified: MDD, four trials (n = 189), three of which investigated memantine augmentation for antidepressants; and BD, two trials (n = 262), bothabout memantine augmentation for mood stabilizers Qualitätsbewertung der Studien: Cochrane risk-of-bias tool
	3. Ergebnisdarstellung <u>Qualität der Studien:</u>  • Memantine was not superior to placebo in all efficacy outcomes. • There were no significant differences in any safety outcomes between memantine and placebo groups.
	4. Fazit der Autoren: Our results suggest that memantine did not demonstrate treatment efficacy for depressive symptoms in MDD and BD patients. However, because our study had some limitations, a long-term study of memantine for depression is needed 5. Kommentare zum Review • Keine Angaben bzw. separate Analysen zur Vortherapie • Patient characteristics differed between the studies, including the severity of symptoms, inclusion criteria, race and ethnicity, and study duration; this could generate heterogeneity when combining data for systematic review and meta-analysis. • All the studies evaluated had short trial durations (mean, 8.33 weeks) → no long-term data • No funnel plot for exploring potential publication bias was used because this technique is generally used only if 10 or more studies are included in a meta-analysis.
Meister R et al., 2016 [26]. Comparative Safety of Pharmacologic	1. Fragestellung We aimed to compare the safety of antidepressants for the treatment of persistent[1] depressive disorder (PDD) with each other and with placebo

Treatments for Persistent Depressive Disorder: A Systematic Review and Network Meta-Analysis	[1] *As the distinction between subtypes of persistent depressive disorder is controversial, inclusion was primarily driven by the duration of the existing depressive disorder of at least two years.*
	2. Methodik Data were analyzed using traditional and network meta-analyses Population: Adults diagnosed with PDD Intervention / Komparator: acute pharmacologic treatments with each other or with placebo Endpunkte: incidence of experiencing any adverse event, specific adverse events and related treatment discontinuations Recherche: Primary search in 2010 and updates in 2013, 2014, and 2016 Anzahl eingeschlossene Studien/Patienten (Gesamt): Thirty-four studies that comprised 4,769 patients and examined 20 individual agents in nine substance classes were included Qualitätsbewertung der Studien: in accordance with the Cochrane Collaboration's Risk of Bias tool that was modified and extended in accordance with the recommendations of the Cochrane Collaboration regarding adverse events and the US Agency for Healthcare Research and Quality (AHRQ)
	3. Ergebnisdarstellung <u>Qualität der Studien</u>: Global methodological quality was rated as low for 13 studies, as unclear for 17 studies and as high for 4 studies Almost all analyzed substance classes were associated with higher discontinuation rates than placebo including tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), antipsychotics, and the serotonin antagonist and reuptake inhibitor (SARI) trazodone. • The odds of experiencing any adverse event were significantly higher for TCAs and serotonin noradrenaline reuptake inhibitors (SNRIs) compared to placebo. • Pairwise comparisons among the substance classes revealed that more patients receiving TCAs or SNRIs experienced any adverse event and that more patients receiving TCAs or the SARI trazodone discontinued treatment. • The complementary treatment with acetyl-l-carnitine showed lower rates of experiencing any adverse event and related discontinuations than all other comparators.

	• TCAs were primarily associated with (anti-)cholinergic and sedating adverse events. • SSRIs primarily showed gastrointestinal adverse events. • Patients treated with the antipsychotic amisulpride were more likely to manifest weight gain and endocrine adverse events. • The comparative evidence for further agents was insufficient or lacking.
	4. Fazit der Autoren: In our systematic review on primary studies investigating the comparative safety of acute treatments of PDD, we demonstrated that substantial differences between both substance classes and individual agents exist. This information may be used to achieve the best possible fit between the effects (both positive and negative) of the agent and the individual needs of the patient. 5. Kommentare zum Review • Keine Subgruppenanalysen durchgeführt: The numbers of included studies, however, were too small to allow sub-analyses • Heterogenität zwischen den Studien
Karyotaki E et al., 2016 [14]. Combining pharmacotherapy and psychotherapy or monotherapy for major depression? A meta-analysis on the long-term effects Siehe auch: **Karyotaki E et al., 2014 [13].**	1. Fragestellung analysis aimed to examine to what extent combined pharmacotherapy with psychotherapy results in a different response to treatment compared to psychotherapy or pharmacotherapy alone in adults with major depression at six months or longer post-randomization
	2. Methodik Population: adult patients with depression Intervention/Komparator: The selected interventions were main psychotherapy interventions combined with antidepressive agents compared to main psychotherapy intervention or antidepressants alone. Psychotherapy was classified into seven different types: behavioral activation, cognitive-behavioral therapy, Interpersonal therapy, problemsolving therapy, psychodynamic therapy, social skills training, and supportive counseling. Endpunkte: treatment response and sustained response Recherche: We conducted a systematic literature search in the biblio- graphic databases of Medline, PsycInfo, Embase and the Cochrane library from database inception to September 1, 2014 Anzahl eingeschlossene Studien/Patienten (Gesamt): 3 randomized controlled trials with 2184 participants

	Qualitätsbewertung der Studien: Cochrane Risk of Bias tool
	3. Ergebnisdarstellung Qualität der Studien: Siehe Tabelle im Anhang! In acute phase treatment, combined psychotherapy with antidepressants outperformed antidepressants alone at six months or longer post randomization in patients with major depressive disorder (OR=2.93, 95%CI 2.15–3.99, p<0.001). Heterogeneity was zero. However, combined therapy resulted in equal response to treatment compared to psychotherapy alone at six months or longer post randomization. As for the maintenance treatment, combined maintenance psychotherapy with antidepressants resulted in better-sustained treatment response compared to antidepressants at six months or longer post randomization (OR=1.69, 95% CI 1.14–2.27, p<0.05). Heterogeneity was zero. Subgruppenanalysen:

Table 4
Effect sizes for combined psychotherapy with antidepressants vs. antidepressants in adults with MDD, acute phase.

Outcomes	N	OR	95%CI[a]	I^2	95%CI	p[b]
Response at 6 months or longer postrandomization	13	2.93*	2.15–3.99	0	0–57	
Subgroups						
Type of psychotherapy						
CBT vs.	6	3.02*	1.74–5.25	0	0–75	0.88
Other	7	2.87*	1.77–4.64	32	0–71	
Risk of bias						
Risk of bias ≤ 3vs.	4	1.66	0.98–2.81	0	0–85	0.17
Risk of bias > 3	5	2.26*	1.35–3.78	13	0–82	
Types of antidepressants						
SSRI	6	2.64*	1.70–4.11	19	0–64	0.51
TCA	6	3.37*	1.90–5.99	0	0–75	
Response at 1 year or longer postrandomization	8	2.23*	1.43–3.41	0	0–68	
Subgroups						
Type of psychotherapy						
CBT vs.	4	3.37*	1.38–8.21	0	0–85	0.29
Other	4	1.94*	1.16–3.23	0	0–85	
Risk of bias						
Risk of bias ≤ 3 vs.	4	1.94*	1.16–3.23	0	0–85	0.29
Risk of bias > 3	4	3.37*	1.38–8.21	0	0–85	
Types of antidepressants						
SSRI	3	1.64	0.84–3.18	0	0–90	0.22
TCA	5	2.84	1.57–5.16	0	0–79	
Sensitivity analysis						
Response at 6 months or longer postrandomization (inpatients excluded)	11	2.98*	2.07–4.29	8	0–63	
Response at 1 year or longer postrandomization (inpatients excluded)	6	1.99*	1.14–3.47	0	0–75	

Subgroup analyses were conducted only in the cases where at least three comparisons were available per group. *N*: Number of comparisons.

* $p < 0.05$.

[a] 95%CI: 95% Confidence Intervals; OR: Odds Ratio; *p*: *p*-value.

[b] *p*-value between groups.

4. Fazit der Autoren: Combined therapy results in a superior enduring effect compared to antidepressants alone in patients with major depression. Psychotherapy is an adequate alternative for combined treatment in the acute phase as it is as effective as combined treatment in the long-term.

Li G et al., 2016 [19].

Vortioxetine versus Duloxetine in the Treatment of Patients with Major Depressive Disorder: A Meta-Analysis of

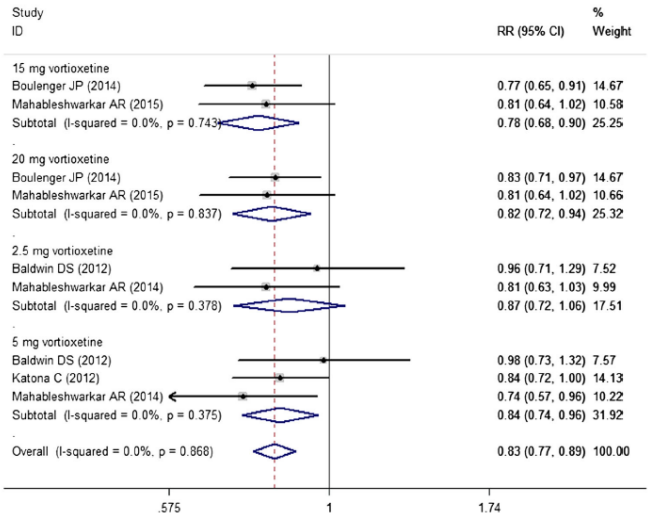
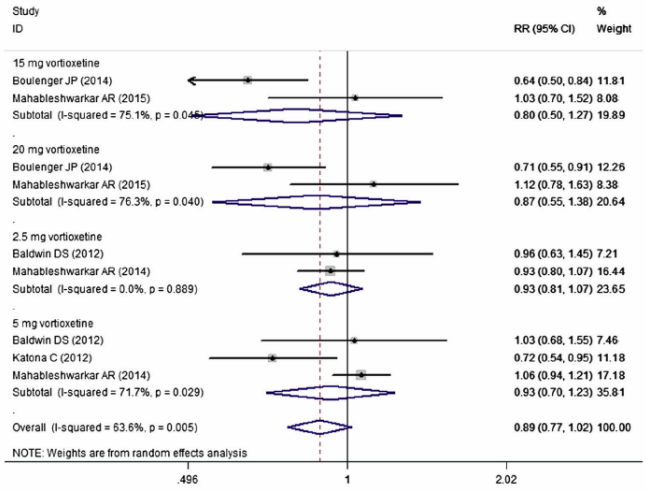
1. Fragestellung

To evaluate the efficacy and tolerability of vortioxetine compared with duloxetine in MDD

2. Methodik

Population: adult patients with a primary diagnosis of MDD

Intervention: vortioxetine
Komparator: duloxetine

Randomized Controlled Trials	Endpunkte: response rate, remission rate, changes from baseline in Montgomery–Asberg Depression Rating Scale (MADRS), Clinical Global Impression–Severity scale (CGI–S), CGI–Improvement scale (CGI–I), 24-item HAM–D (HAM–D24), and Sheehan Disability Scale (SDS) scores. Recherche: Systematische Literaturrecherche von Oktober 2015, und aktualisiert im März 2016 Anzahl eingeschlossene Studien/Patienten (Gesamt): A total of five RCTs involving 2287 patients Qualitätsbewertung der Studien: Jadad Score
	3. Ergebnisdarstellung <u>Qualität der Studien</u>: All studies had a Jadad Score of 4 Pooled results showed that duloxetine was associated with a higher response rate than vortioxetine, as well as showing a similar remission rate with vortioxetine (siehe figure 2 und 3 unten). **Fig. 2** Forest plot showing the effect comparison of vortioxetine and duloxetine on response rate (RR)  **Fig. 3** Forest plot showing the effect comparison of vortioxetine and duloxetine on remission rate (RR) 

The changes from baseline in the Montgomery–Asberg Depression Rating Scale (MADRS), 24-item Hamilton Rating Scale for Depression (HAM–D24), Clinical Global Impression–Improvement scale (CGI–I), CGI–Severity scale (CGI–S), Sheehan Disability Scale (SDS), and Hamilton Anxiety Rating Scale (HAM–A) scores were significantly greater in the duloxetine group than in the vortioxetine group (siehe figure 4 unten).

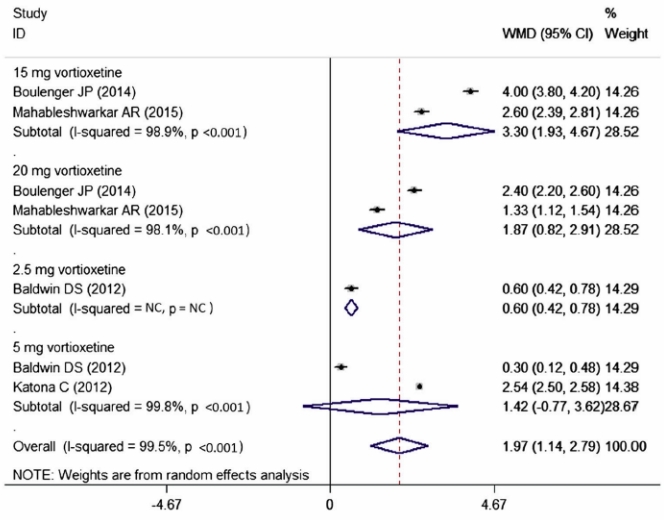


Fig. 4 Forest plot showing the effect comparison of vortioxetine and duloxetine on MADRS score. *MADRS* Montgomery–Åsberg Depression Rating Scale, *NC* heterogeneity test not conducted since there was only one study, *WMD* weighted mean difference

- The incidence of treatment-emergent adverse events was significantly higher in the duloxetine group than in the vortioxetine group (RR 0.88, 95 % CI 0.82–0.94; p<0.001).
- Compared with duloxetine, vortioxetine induced a significantly lower incidence of common adverse events, including nausea (RR 0.70, 95 % CI 0.56–0.87; p = 0.001), diarrhea (RR 0.74, 95 % CI 0.57–0.97; p = 0.030), dry mouth (RR 0.50, 95 % CI 0.39–0.63; p<0.001), dizziness (RR 0.51, 95 % CI 0.37–0.69; p\0.001), fatigue (RR 0.45, 95 % CI 0.32–0.64; p<0.001), hyperhidrosis (RR 0.35, 95 % CI 0.23–0.55; p<0.001), somnolence (RR 0.33, 95 % CI 0.21–0.52; p<0.001), constipation (RR 0.47, 95 % CI 0.34–0.64; p\0.001), insomnia (RR 0.65, 95 % CI 0.46–0.92; p = 0.016), and decreased appetite (RR 0.24, 95 % CI 0.09–0.69; p = 0.008). However, nasopharyngitis occurred at a higher frequency with vortioxetine than duloxetine (RR 2.25, 95 % CI 1.25–4.06; p = 0.007).

4. Fazit der Autoren: Duloxetine was more effective but less well tolerated than vortioxetine in MDD. Considering the potential limitations of this meta-analysis, more large-scale RCTs are needed to confirm these findings.

5. Kommentare zum Review
   - Subgruppenanalysen lediglich zur Dosierung. Keine Angaben bzw. separate Analysen hinsichtlich der Vortherapie

Brignone M et al., 2016 [2]. Efficacy and tolerability of switching therapy to vortioxetine versus other antidepressants in patients with major depressive disorder	1. Fragestellung To assess the relative efficacy and tolerability of vortioxetine against different antidepressant monotherapies in patients with major depressive disorder (MDD) with inadequate response to selective serotonin reuptake inhibitor (SSRI) or serotonin–norepinephrine reuptake inhibitor (SNRI) therapy.
	2. Methodik Population: adult patients (≥18 years) of any race or gender. Patients with MDD, dysthymia, or subsyndromal depression were included. Patients with MDD who had failed to respond to a prior antidepressant. → *Patients classified as having failed treatment or as having an 'inadequate response' were eligible for inclusion in the review; inadequate response was measured as a failure to reduce depression rating scores by ≥50%, in accordance with guidelines.* Intervention / Komparator: The review included studies evaluating switch therapies, dose up-titrations or reassessment of initial therapy for different antidepressant monotherapies. The interventions assessed across the studies comprised various antidepressant classes commonly used in clinical practice, such as: SSRIs, SNRIs, monoamine oxidase inhibitors, tricyclic antidepressants, tetracyclic antidepressants, or non-SSRI antidepressants. Endpunkte: remission rate, number of patients in each treatment group who withdrew before completion of the study due to AEs Recherche: Systematic literature search from January 1980 to 27 March 2014. Anzahl eingeschlossene Studien/Patienten (Gesamt): Of 27 studies meeting the inclusion criteria. Qualitätsbewertung der Studien: according to the National Institute of Health and Care Excellence checklist
	3. Ergebnisdarstellung Qualität der Studien: Siehe Tabelle im Anhang! *Hinweis*: adjustierter indirekter Vergleich Three studies contributed to an evidence network for quantitative assessment comparing vortioxetine with agomelatine, sertraline, venlafaxine XR, and bupropion SR. Vortioxetine had a statistically significantly higher remission rate than agomelatine (risk difference [RD]: -11.0% [95% CI: -19.4; -2.6]), and numerically higher remission

	rates than sertraline, venlafaxine, and bupropion. Withdrawal rates due to AEs were statistically significantly lower for vortioxetine than sertraline (RD: 12.1% [95% CI: 3.1; 21.1]), venlafaxine XR (RD: 12.3% [95% CI: 0.8; 23.8]), and bupropion SR (RD: 18.3% [95% CI: 6.4; 30.1]).
	4. Fazit der Autoren: The current systematic literature review found a few high quality switch studies assessing monotherapies in patients with MDD with inadequate response to SSRI/SNRIs. ITCs indicated that switching to vortioxetine leads to numerically higher remission rates compared with other antidepressants. Vortioxetine is a well-tolerated treatment, showing statistically lower withdrawal rates due to AEs compared with other antidepressants. Vortioxetine is a relevant therapeutic alternative in patients experiencing inadequate response to prior SSRI or SNRI therapy. 5. Kommentare zum Review • There is also a low generalizability across patients experiencing inadequate response to MDD therapy, both in terms of the number of previous depressive episodes and different first-line treatment options used by patients, making comparisons between trials difficult → Variation between studies in terms of the prior therapy status was evident, including the definitions of inadequate response and duration of prior therapy
Henssler J et al., 2016 [10]. Combining Antidepressants in Acute Treatment of Depression: A Meta-Analysis of 38 Studies Including 4511 Patients	1. Fragestellung We conducted a systematic review and meta-analysis aimed at determining efficacy and tolerability of combination therapy.
	2. Methodik Population: adult patients suffering from acute depression Intervention/Komparator: combination therapy → siehe Details beim Ergebnisteil Endpunkte: primary outcome was standardized mean difference (SMD), secondary outcomes were response, remission, and dropouts Recherche: MEDLINE, Embase, PsycINFO, and CENTRAL databases were systematically searched through March 2014 Anzahl eingeschlossene Studien/Patienten (Gesamt): 38 studies were eligible, including 4511 patients. Qualitätsbewertung der Studien: Cochrane's risk of bias tool

	3. Ergebnisdarstellung Qualität der Studien: 11 Studien mit einem niedrigen Verzerrungspotenzial; 27 Studien mit einem hohen bzw. unklaren Verzerrungspotenzial. • Combination treatment was statistically, significantly superior to monotherapy (SMD 0.29; 95% CI 0.16 to 0.42). • During monotherapy, slightly fewer patients dropped out due to adverse events (n.s.). → Studies were heterogeneous (I^2 = 63%), and there was indication of moderate publication bias, but results remained robust across pre-specified secondary outcomes and subgroups, including analyses restricted to randomized controlled trials and low risk of bias studies. Sensitivity and Subgroup Analyses: • The effect remained robust across subgroup analyses restricted to randomized, doubleblind trials (SMD 0.33; 95% CI 0.11 to 0.54, P = 0.003) to low risk of bias-trials (SMD 0.36; 95% CI 0.13 to 0.59, P = 0.002), to trials excluding patients with BD (SMD 0.30; 95% CI 0.07 to 0.53, P = 0.01), and to RCTs of MDD patients treated with standard doses (SMD 0.25; 95% CI 0.04 to 0.46, P = 0.02). In trials limited to non-responders, the direction of effect remained but effect sizes were lower. Post-hoc analyses: • Another post hoc analysis revealed similar effects in samples of only patients with MDD (SMD 0.30; 95% CI 0.15 to 0.44) (23 studies). • The difference between combination and monotherapy was more pronounced in treatment-naive patients than in patients with treatment-resistant depression (TRD) (SMD 0.41; 95% CI 0.10 to 0.72) [6 studies], compared with 0.13; 95% CI –0.18 to 0.44 [8 studies]; randomized, double-blind studies, patients with MDD only) (siehe für weitere Analysen Tabelle 2!)

Table 2. Results and outcomes across subgroup analyses

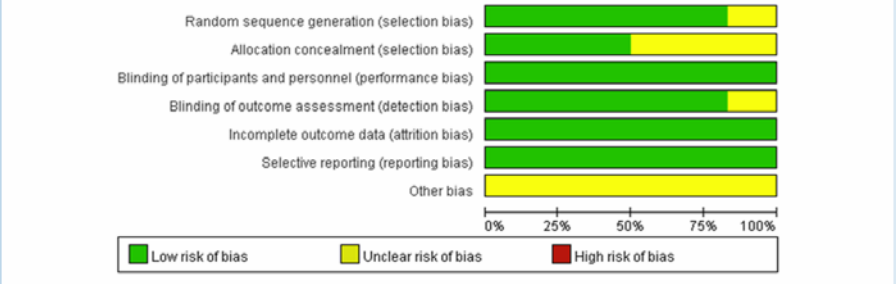
	Primary outcome	Secondary outcomes				
	SMD	Remission	Response	SMD at study endpoint	Dropouts	Dropouts due to AE
Results	SMD (95% CI)	OR (95% CI)	OR (95% CI)	SMD (95% CI)	OR (95% CI)	OR (95% CI)
Whole sample (38 studies)	0.29 (0.16 to 0.42); $n = 4342$ (36 studies)	1.63 (1.24 to 2.08); $n = 3884$ (27 studies)	1.68 (1.32 to 2.14); $n = 3769$ (29 studies)	−0.20 (−0.37 to −0.03); $n = 2989$ (20 studies)	0.82 (0.62 to 1.08); $n = 2044$ (29 studies)	0.90 (0.53 to 1.53); $n = 2857$ (17 studies)
rand.db. (20 studies)	0.33 (0.11 to 0.54); $n = 1643$ (18 studies)	1.63 (1.07 to 2.48); $n = 1287$ (12 studies)	2.38 (1.50 to 3.77); $n = 1130$ (12 studies)	−0.13 (−0.61 to 0.36); $n = 441$ (6 studies)	0.79 (0.59 to 1.07); $n = 1405$ (16 studies)	0.87 (0.51 to 1.48); $n = 883$ (10 studies)
Non(rand.db.) (18 studies)	0.27 (0.09 to 0.44); $n = 2699$ (18 studies)	1.65 (1.15 to 2.37); $n = 2597$ (15 studies)	1.35 (1.04 to 1.75); $n = 2639$ (17 studies)	−0.23 (−0.41 to −0.05); $n = 2548$ (14 studies)	1.03 (0.49 to 2.19); $n = 639$ (13 studies)	0.89 (0.34 to 2.34); $n = 1974$ (7 studies)
rand.db. nonresponder (8 studies)	0.13 (−0.18 to 0.44); $n = 808$ (8 studies)	1.22 (0.71 to 2.07); $n = 713$ (6 studies)	1.53 (0.87 to 2.68); $n = 619$ (4 studies)	0.01 (−0.81 to 0.82); $n = 157$ (4 studies)	0.65 (0.37 to 1.14); $n = 450$ (5 studies)	0.94 (0.23 to 3.83); $n = 156$ (3 studies)
Low risk of bias (11 studies)	0.30 (0.09 to 0.50); $n = 1773$ (11 studies)	1.84 (1.18 to 2.89); $n = 1537$ (8 studies)	2.00 (1.27 to 3.14); $n = 1528$ (10 studies)	−0.21 (−0.54 to 0.11); $n = 975$ (4 studies)	0.73 (0.52 to 1.04); $n = 956$ (8 studies)	0.72 (0.39 to 1.32); $n = 1408$ (8 studies)
High /unknown risk of bias (27 studies)	0.25 (0.09 to 0.42); $n = 2569$ (25 studies)	1.54 (1.08 to 2.18); $n = 2347$ (19 studies)	1.57 (1.16 to 2.12); $n = 2241$ (19 studies)	−0.19 (−0.39 to 0.01); $n = 2014$ (16 studies)	0.99 (0.63 to 1.54); $n = 1088$ (21 studies)	1.25 (0.67 to 2.34); $n = 1449$ (9 studies)
Exclusion of patients with bipolar disorder (12 studies)	0.30 (0.07 to 0.53); $n = 1661$ (12 studies)	2.13 (1.28 to 3.55); $n = 1661$ (12 studies)	1.59 (1.00 to 2.53); $n = 1210$ (8 studies)	−0.17 (−0.47 to 0.12); $n = 1114$ (6 studies)	0.84 (0.56 to 1.27); $n = 700$ (8 studies)	0.61 (0.29 to 1.27); $n = 1253$ (7 studies)
Patients with MDD rand.db. (15 studies)	0.25 (0.04 to 0.46); $n = 1382$ (14 studies)	1.63 (1.07 to 2.48); $n = 1287$ (12 studies)	1.94 (1.27 to 2.97); $n = 869$ (8 studies)	−0.14 (−0.55 to 0.26); $n = 499$ (7 studies)	0.78 (0.55 to 1.09); $n = 1019$ (11 studies)	0.96 (0.50 to 1.85); $n = 680$ (8 studies)

Primary outcome: SMD > 0 in favour of combination. Secondary outcomes: OR > 1 designates superiority of combination treatment; SMD < 0 designates superiority of combination treatment. Study number in the first column refers to the number of studies in a subgroup: for example, there are 20 randomized double-blind studies. Note, depending on design specifics, studies from column 1 may not be included in all outcome analyses (for example, only 10 randomized double-blind studies reported data on the number of dropouts due to adverse effects).
AE = adverse events; MDD = major depressive disorder; rand.db. = randomized, double-blind trials; SMD = standardized mean difference

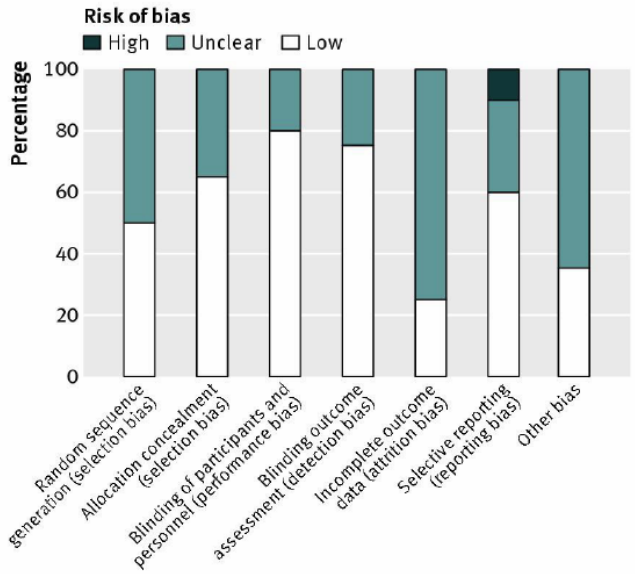
4. Fazit der Autoren: Combining ADs seems to be superior to monotherapy with only slightly more patients dropping out. Combining a reuptake inhibitor with an antagonist of presynaptic a2-autoreceptors seems to be significantly more effective than other combinations. Overall, our search revealed a dearth of well-designed studies.

5. Kommentare zum Review

- this meta-analysis included studies covering different patient populations e.g.:
  - Diagnoses of other psychiatric disorders, as well as comorbid medical conditions, were no exclusion criteria. Studies specifically on bipolar disorder (BD) were excluded.
  - Both trials on first-line treatment and trials among patients with resistance to previous AD treatment(s) were included. → siehe Ergebnisteil!
- I^2 values indicated substantial heterogeneity of effects
- Some of the trials (N = 10) required nonresponse to an initial period of AD monotherapy. Trials consisted of AD monotherapy of this agent (in continuation), compared with add-on therapy with an additional AD. Therefore, dropouts due to adverse effects may have been decreased in the monotherapy group, as patients may

	have dropped out during the pre-trial period.
Huang KL et al., 2014 [11]. Comparison of agomelatine and selective serotonin reuptake inhibitors/ serotonin–norepinephrine reuptake inhibitors in major depressive disorder: A meta-analysis of head-to-head randomized clinical trials	1. Fragestellung This meta-analysis comprehensively shows the efficacy, acceptability, and safety of agomelatine in comparison with SSRIs and SNRIs used as antidepressants in MDD
	2. Methodik Population: Patients with MDD Intervention: Agomelatine Komparator: SSRI or SNRI Endpunkte: number of patients with a treatment response (primärer Endpunkt); number of patients who had achieved remission, Leeds Sleep Evaluation Questionnaire (LSEQ) subjective sleep score changes, the difference between post- and pretrial symptom mean scores, acceptability Recherche: The database search for this study included PubMed (from 1966 to 23 July 2013), CINAHL (from 2007 to 23 July 2013), PsycINFO (from 1998 to 23 July 2013), EMBASE (from 1974 to 23 July 2013), and the Cochrane Central Register of Controlled Trials (CENTRAL; 2013, Issue 5). Anzahl eingeschlossene Studien/Patienten (Gesamt): The meta-analysis included six head-to-head trials involving 1871 patients Qualitätsbewertung der Studien: Cochrane risk of bias tool
	3. Ergebnisdarstellung Qualität der Studien: All included studies were RCTs. **Figure 2.** Overall risk of bias in the individual studies (n = 6).  • In the acute phase, agomelatine had higher response rates (relative risk (RR) 1.08, 95% confidence interval (CI) 1.02–1.15) compared to SSRIs and SNRIs. • In the remission analysis, only acute remission rates (RR 1.12, 95% CI 1.01–1.24) significantly differed. • The action of agomelatine was superior on the Leeds Sleep

	Evaluation Questionnaire-Quality of Sleep score (mean difference 4.05, 95% CI 0.61–7.49). • Discontinuation due to inefficacy did not differ between agomelatine and SSRIs/SNRIs (RR 0.74, 95% CI 0.42–1.28). • Compared to SSRIs and SNRIs, however, agomelatine revealed a lower rate of discontinuation due to side effects (RR 0.38, 95% CI 0.25–0.57).
	4. Fazit der Autoren: Agomelatine has significantly higher efficacy and potential acceptability compared to SSRIs and SNRIs when treating MDD. However, the difference in efficacy is not considered clinically relevant. Because of its unique chronobiotic effects, agomelatine may be useful for the management of some MDD patients with circadian disturbance 5. Kommentare zum Review • Keine Angaben bzw. separate Analysen zur Vortherapie
Taylor D et al., 2014 [34]. Antidepressant efficacy of agomelatine: meta-analysis of published and unpublished studies	1. Fragestellung To systematically review published and unpublished efficacy studies of agomelatine in people with depression.
	2. Methodik Population: Adults with depression Intervention: Agomelatine Komparator: placebo and/or other antidepressant Endpunkt: treatment response, remission, tolerability Recherche: From inception to 2013: Embase, Medline, Cochrane Central Register of Controlled Trials, and PubMed, with the last search performed in March 2013. Anzahl eingeschlossene Studien/Patienten (Gesamt): 20 trials with 7460 participants Qualitätsbewertung der Studien: Cochrane risk of bias tool
	3. Ergebnisdarstellung <u>Qualität der Studien</u>:

	 **Fig 2** Risk of bias across studies on antidepressant efficacy of agomelatine Agomelatine was significantly more effective than placebo with an effect size (SMD) of 0.24 (95% confidence interval 0.12 to 0.35) and relative risk of response 1.25 (1.11 to 1.4). Compared with other antidepressants, agomelatine showed equal efficacy (SMD 0.00, −0.09 to 0.10). → Significant heterogeneity was uncovered in most analyses, though risk of bias was low. Published studies were more likely than unpublished studies to have results that suggested advantages for agomelatine.
	4. Fazit der Autoren: Agomelatine is an effective antidepressant with similar efficacy to standard antidepressants. Published trials generally had more favourable results than unpublished studies. 5. Kommentare zum Review • Keine Angaben bzw. separate Analysen zur Vortherapie
Bschor T et al., 2016 [3]. Switching the Antidepressant after nonresponse in adults with major depression.	1. Fragestellung To compare the efficacy of switching to a new antidepressant with continuation of the first antidepressant.
	2. Methodik Population: Patients with MDD and nonresponse[1] Intervention/Komparator: switching vs. continuation therapy → siehe für Details Ergebnisteil! Endpunkte: • Primärer Endpunkt/Ziel: comparison efficacy between switch

	and continuation arms of the included studies • Sekundäre Endpunkte: Ansprechen, Remission, Verträglichkeit Recherche: Systematische Literaturrecherche im März 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): Es wurden 4 Studien in die sogenannte ,,strict analysis'' eingeschlossen und insgesamt 8 Studien für die breite Analyse. Qualitätsbewertung der Studien: Cochrane risk of bias tool *[1] nonresponse = <30% improvement of every participant to a first treatment period of at least 2 weeks at standard or higher doses*
	3. Ergebnisdarstellung Qualität der Studien: 4 Studien mit niedrigem Verzerrungspotenzial und 4 Studien mit hohen/unklarem Verzerrungspotenzial. **Table 1. Characteristics of Studies Included In a Systematic Meta-Analysis Comparing Switching to a New Antidepressant Versus Continuation of the Initial Antidepressant in Patients With Major Depressive Disorder After Nonresponse to Antidepressant Monotherapy** Study/First Author; Year of Publication; Initial and Continuation Antidepressant; Switch Antidepressant; Follow-Up Time (wk); N After Randomization[a]; Dose Escalation Allowed in the Continuation Arm?; Low Risk of Bias According to Cochrane Collaboration Tool for Assessing Risk of Bias? Ferreri[28] 2001 Fluoxetine Mianserin 6 71 No Yes Corya[29] 2006 Venlafaxine Fluoxetine 12 119 No No Souery[27] 2011 Desipramine or citalopram Desipramine or citalopram 4 59 No Yes Shelton[30] 2005 Nortriptyline Fluoxetine 8 210 No No Romera[32] 2012 Escitalopram Duloxetine 4 566 Yes Yes Bose[33] 2012 Escitalopram Duloxetine 8 472 Yes Yes Petrescu[34] 2014[b] Any SSRI Duloxetine 8 52 Yes No Zhu[31] 2003 Various SSRIs Mirtazapine 6 78 Yes No [a]A total of 1,627 patients were included in the meta-analysis. [b]Published as abstract only. Abbreviation: SSRI = selective serotonin reuptake inhibitor. • In beiden Analysen (,,strict analysis'' und ,,broad analysis'') zeigte sich keine Überlegenheit einer ,,switching'' Therapie gegenüber einer weiterführenden Behandlung. → primäres Ziel des SR! • In allen sekundären Endpunkten (Ansprechen und Remission) bestätigten das Ergebnis der Primäranalyse. • Keine Unterschiede hinsichtlich der Verträglichkeit
	4. Fazit der Autoren ***Conclusions:*** There is a dearth of randomized controlled trials investigating switching. There is no high-level evidence that switching the antidepressant is effective when compared to simply continuing the initial antidepressant. Since there are better treatment options than switching, physicians should be cautious to switch antidepressants.
Gartlehner G et al., 2015 [6]. Nonpharmacological Versus Pharmacological Treatments for Adult Patients With	1. Fragestellung KQ 2a. In adult patients with MDD who did not achieve remission following an initial adequate trial with one SGA, what is the comparative effectiveness of second-step therapies? KQ 2b. Does comparative treatment effectiveness vary by MDD severity? KQ 3a. In adult patients with MDD, what are the comparative risks of

Major Depressive Disorder	harms of these treatment options - For those who did not achieve remission following an initial adequate trial with an SGA?
	2. Methodik Population: Adult (18 years or older) outpatients of all races and ethnicities with MDD during either an initial treatment attempt or a second treatment attempt in patients who did not have remission following an initial adequate trial with an SGA. Intervention/Komparator: For patients with acute-phase MDD and an initial treatment attempt, we were interested in common depression-focused psychotherapies, common CAM interventions, and exercise 1. as monotherapies 2. in combination with one another, or 3. in combination with SGAs. For patients who did not achieve remission following an initial adequate trial with an SGA, we were also interested in second-step therapies that involve an eligible intervention (whether as a monotherapy or a combination therapy). Table 4 presents interventions that were eligible for this report.

Table 4. Eligible interventions for major depressive disorders

Second-Generation Antidepressants[a]	Common Depression-Focused Psychotherapies	Complementary and Alternative Medicines	Exercise	Other Pharmacotherapies for Combination or Augmentation
• Bupropion • Citalopram • Desvenlafaxine • Duloxetine • Fluoxetine • Escitalopram • Fluvoxamine • Levomilnacipran • Mirtazapine • Nefazodone • Paroxetine • Sertraline • Trazodone • Venlafaxine • Vilazodone • Vortioxetine	• Behavioral therapies/behavior modification • Cognitive behavioral therapies • Integrative therapies (e.g., interpersonal therapy) • Psychodynamic therapies • Third-wave cognitive behavioral therapies	• Acupuncture • Meditation (e.g., mindfulness-based stress reduction) • Omega-3 fatty acids • S-adenosyl-L-methionine (SAMe) • St. John's wort (Hypericum perforatum) • Yoga	Any formal exercise program	• Atypical antipsychotics (aripiprazole, asenapine maleate, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone) • Psychostimulants (amphetamine-dextroamphetamine, armodafinil, dexmethylphenidate, dextroamphetamine, lisdexamfetamine, methyphenidate, modafinil) • Buspirone • Levothyroxine (T4) • Lithium • Pindolol • Triiodo-thyronine (T3)

FDA = Food and Drug Administration; SAMe = S-adenosyl-L-methionine; SGA = second-generation antidepressant
[a] SGAs approved for treatment of MDD by the U.S. FDA.

Endpunkte:

- Benefits: response to treatment, remission, speed of response, speed of remission, relapse, quality of life, functional capacity, reduction of suicidal ideas or behaviors, reduction of hospitalization
- Harms: overall adverse events, withdrawals because of adverse events, serious adverse events, specific adverse events (including hyponatremia, seizures, suicidal ideas or behaviors, hepatotoxicity, weight gain, gastrointestinal symptoms, sexual

	side effects), or drug interactions (pharmacological and complementary and alternative treatments) Recherche: MEDLINE® (via PubMed®), Embase®, the Cochrane Library, AMED (Allied and Complementary Medicine Database), PsycINFO®, and CINAHL (Cumulative Index to Nursing and Allied Health Literature) from January 1, 1990, through January 13, 2015. Anzahl eingeschlossene Studien/Patienten (Gesamt): Overall, we included 44 trials reported in 55 published articles. Of these, 42 trials pertained to KQ 1a and 5 to KQ 1b. Two trials pertained to KQ 2a, and no trials were identified for KQ 2b. In addition, of the 44 trials, 43 trials pertained to KQ 3a and 1 to KQ 3b; 3 pertained to KQ 4. For network meta-analyses, we included data from 85 additional published trials and 27 unpublished trials. These trials addressed comparisons of interventions of interest that did not meet eligibility criteria for this report; they did, however, provide common comparators that we could use for network meta-analyses. Qualitätsbewertung der Studien: Two investigators independently selected, extracted data from, and rated risk of bias of studies. We graded strength of evidence based on AHRQ guidance established for the Evidence-based Practice Centers. This approach incorporates five key domains: risk of bias, consistency, directness, precision, and reporting bias. Grades (high, moderate, low, insufficient) reflect the strength of the body of evidence for a specific outcome on the comparative benefits and harms of the interventions in this review. During the protocol development, we asked the Technical Expert Panel and the Key Informants to rank the relative importance of outcomes following a process proposed by the GRADE (Grading of recommendations Assessment, Development and Evaluation) Working Group. We graded only those outcomes that Technical Expert Panel members and Key Informants deemed as important or critical for decision-making.
	3. Ergebnisdarstellung <u>Qualität der Studien</u>: Across all interventions, we graded the strength of evidence for benefits as moderate for only one comparison—namely, SGAs compared with CBT. Results from trials of this comparison indicate that SGAs and CBT have similar effectiveness regarding symptomatic relief in patients with mild to severe MDD. For risk of harms, we graded the strength of evidence as moderate for some outcomes of three comparisons—namely, SGAs compared with CBT, acupuncture, and St. John's wort. Patients treated with SGAs had a higher risk of experiencing adverse events or discontinuing treatment because of adverse events than patients treated with CBT, acupuncture, or St. John's wort. The evidence is insufficient to draw conclusions about differences in serious adverse events, such as

	suicidal ideas and behavior. → Siehe auch Ergebnisteil! **Second-Step Therapy: Effectiveness and Harms of Switching or Augmenting Treatment Options for Patients With Major Depressive Disorder** • **Switch:** Second-Generation Antidepressant Versus Second-Generation Antidepressant: Results from two direct comparisons of second-step therapies involving 1,123 patients who were switched to different SGAs indicate no substantial differences in response rates between SGAs (moderate SOE). Results from one direct comparison involving 727 patients indicate no substantial difference in remission rates or in the decrease in depressive severity between SGAs (low SOE). Likewise, results from the same direct comparison of 727 patients indicate no significant difference in overall risk of adverse events (low SOE), rates of discontinuation because of adverse events (moderate SOE), overall risk of serious adverse events (low SOE), and suicidal ideas or behaviors (low SOE). Second-Generation Antidepressant Versus Cognitive Therapy: Results from one direct comparison of second-step therapies involving 122 patients who were assigned to switch to a different SGA or to CT indicate no substantial differences in rates of response or remission or in the decrease in depressive severity (low SOE). In addition, rates of discontinuation because of adverse events (low SOE) were similar between SGAs and CT. Second-Generation Antidepressant Versus Complementary and Alternative Medicine or Exercise: We did not find any eligible switch evidence comparing an SGA strategy with either CAM or exercise. • **Augment:** Second-Generation Antidepressant Versus Second-Generation Antidepressant: Results from one direct comparison of second-step therapies involving 565 patients indicate no substantial differences in rates of response or remission between SGAs (low SOE). However, results from one direct comparison involving 565 patients indicate a greater decrease in depressive severity after adding bupropion than buspirone (low SOE). In addition, adding bupropion led to lower rates of discontinuation because of adverse events (moderate SOE) but similar rates of serious adverse events (low SOE) and suicidal ideas or behaviors (low SOE) compared with adding buspirone. Second-Generation Antidepressant Versus Cognitive Therapy: Results from one direct comparison of second-step therapies involving 182 patients whose treatment was augmented with a

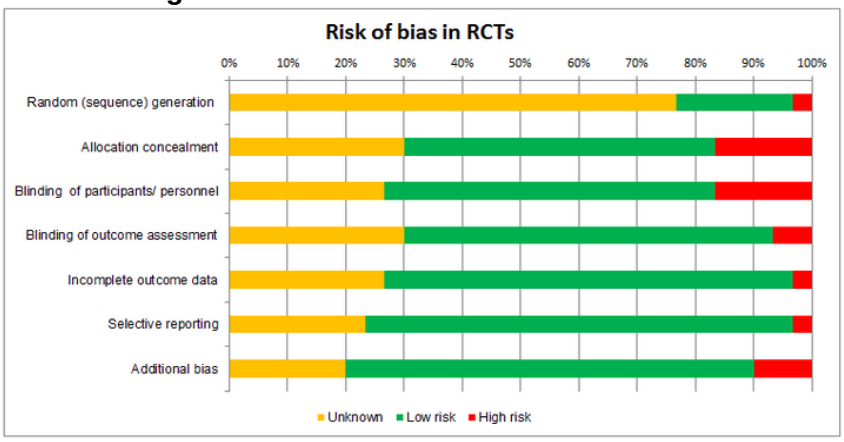
	second medication versus augmented with CT indicate no substantial differences in rates of response or remission, or in the decrease in depressive severity (low SOE). The same results also indicate no significant differences in rates of discontinuation because of adverse events (low SOE) or overall risk of serious adverse events (low SOE). **Severity as a Moderator of Comparative Treatment Effectiveness of Second-Step Therapies:** One industry-supported secondary analysis involving 396 patients found an insignificant trend toward differences in remission rates for those with severe depression (compared with moderate depression). In contrast, a second secondary analysis involving 727 patients, which was government funded, found that having mild or moderate rather than severe depression did not change the likelihood of remitting after treatment with one versus another SGA (insufficient evidence).
	4. Fazit der Autoren: (…) For second-step therapies, although evidence is limited, no clear benefit emerges to suggest that either switching to a particular SGA or CT, or augmenting with a particular medication or CT, is preferable. Available data suggest that switching to another SGA, switching to CT, or augmenting with a particular medication or CT are all reasonable options. The more important decision appears to be simply to try a different evidence-based approach.
Song GM et al., 2015 [33]. Treatment of Adults With Treatment-Resistant Depression: Electroconvulsive Therapy Plus Antidepressant or Electroconvulsive Therapy Alone? Evidence From an Indirect Comparison Meta-Analysis	1. Fragestellung To assess the potential of ECT plus antidepressant compared with ECT alone by undertaking an indirect comparison meta-analysis.
	2. Methodik Population: adult patients were diagnosed as TRD Intervention: ECT plus antidepressant/ECT alone Komparator: Antidepressant alone Endpunkte: deterioration and somatization Recherche: Databases from PubMed, ISI Web of Science, CENTRAL, Clinicaltrials.gov, EMBASE, CBM (China Biomediccal Literatures Database), and CNKI (China National Knowledge Infrastructure) were searched for relevant studies through November 21, 2014 Anzahl eingeschlossene Studien/Patienten (Gesamt): A total of 17

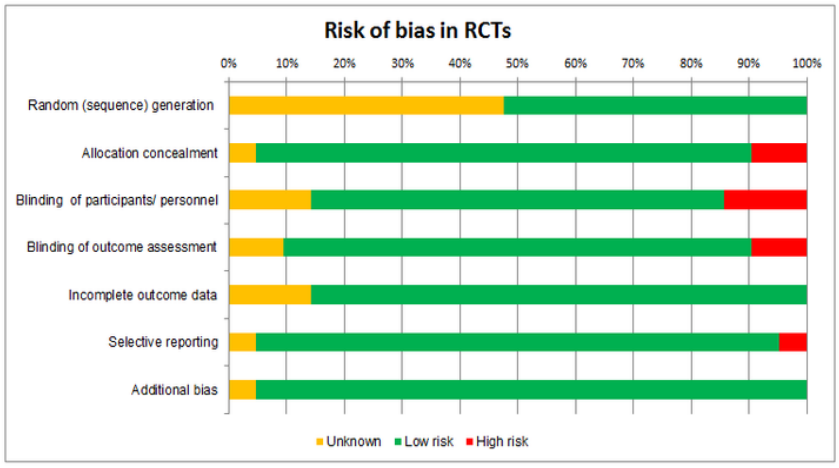
	studies which including 13 studies regarding ECT plus antidepressant versus antidepressant alone and 4 studies concerning ECT versus antidepressant alone containing a total of 1098 patients were incorporated into this meta-analysis Qualitätsbewertung der Studien: Cochrane Collaboration's tool for risk of bias assessment
	3. Ergebnisdarstellung Qualität der Studien: According to the assessment of risk of bias for each study, no study was classified into grade A for overall quality of methodology, 13 studies were rated as B grade and 4 studies were rated as C. • The head-to-head comparison suggested that response rate can be improved in the ECT plus antidepressant (RR, 1.82; 95% CI, 1.55–2.14) and ECT alone group (RR, 2.24, 95% CI, 1.51–3.33) compared with antidepressant alone, respectively. • Adverse complications including memory deterioration and somatization were not significantly increased except incidence of memory deterioration in ECT plus antidepressant in the 4th weeks after treatment (RR, 0.09, 95% CI, 0.02–0.49). • Indirect comparison meta-analysis showed that no significant differences were detected in response rate and memory deterioration between ECT plus antidepressant and ECT alone. However, ECT plus antidepressant increased the incidence of memory deterioration relative to ECT alone.
	4. Fazit der Autoren: There exist insufficient high-quality evidence applicable in the current literature regarding the effectiveness and safety of ECT combined with antidepressant relative to ECT alone for the treatment of patients with TRD. Hence, the findings from this indirect comparison meta-analysis are by no means definitive. Nevertheless, the findings suggested that ECT combined with antidepressant cannot effectively improve the clinical outcomes of patients with TRD compared with ECT alone. In contrast, ECT combined with antidepressant will increase the incidence of memory deterioration relative to ECT alone in the 4th weeks after treatment. In conclusion, the regime of ECT plus antidepressant should not be prior recommended to treat the patients with TRD relative to ECT alone. 5. Kommentare zum Review • small number of eligible studies were included to assess the potential of ECT versus antidepressant alone • In all of the trials included in the study, no study was classified as grade A and 4 studies were rated as grade C • No definitive instruments for assessed the status of adverse

	actions including memory deterioration and somatization symptom were described in all eligible studies and the pooled results may be impaired
Maneeton et al., 2013 [24]. Efficacy, tolerability, and acceptability of bupropion for major depressive disorder: a meta-analysis of randomized–controlled trials comparison with venlafaxine	1. Fragestellung The purpose of this meta-analysis was to determine the efficacy, acceptability, and tolerability of bupropion and venlafaxine therapies for adults with major depressive disorder (MDD).
	2. Methodik Population: adult patients with MDD Intervention: bupropion Komparator: venlafaxine Endpunkte: severity of depression; response rate; remission rate; overall discontinuation rate; or discontinuation rate due to adverse events. Recherche: searches of MEDLINE, EMBASE, CINAHL, PsycINFO, and Cochrane Controlled Trials Register were conducted in February 2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): A total of 1,117 participants in three RCTs were included Qualitätsbewertung der Studien: Cochrane's bias tool
	3. Ergebnisdarstellung Qualität der Studien: Since all trials had the low-risk of biases, all their data were analyzed. • The pooled mean changed scores of the bupropion-treated group were comparable to those of the venlafaxine-treated group (n.s.). • The overall response and remission rates were similar. • The pooled overall discontinuation rate and discontinuation rate due to adverse events were not different between groups.
	4. Fazit der Autoren: According to the limited data obtained from three RCTs, bupropion XL is as effective and tolerable as venlafaxine XR for adult patients with MDD. Further studies in this area should be conducted to confirm these findings. 5. Kommentare zum Review • small number of eligible trials • Keine Angaben bzw. separaten Auswertungen hinsichtlich der Vortherapie

Zhou X et al., 2015 [37]. Atypical Antipsychotic Augmentation for Treatment Resistant Depression: A Systematic Review and Network Meta-Analysis Siehe auch: **Zhou X et al., 2015 [38] und Wen XJ et al., 2014 [35].**	1. Fragestellung We performed a network meta-analysis, which integrates direct and indirect evidence from randomized controlled trials (RCTs), to investigate the comparative efficacy and tolerability of adjunctive atypical antipsychotics for treatment-resistant depression (TRD).
	2. Methodik Population: adult patients (aged more than 18 years) diagnosed with a current episode of major depressive disorder according to standard diagnostic interviews → patients who had an inadequate response to at least one course of conventional antidepressant treatment prior to enrollment in the study Intervention: adjunctive atypical antipsychotic medication Komparator: a different type or different dosage of the adjunctive atypical antipsychotic or against an adjunctive placebo Endpunkte: one or more outcome(s) of depressive symptoms in acute treatment and tolerability → siehe Details in Ergebnisteil! Recherche: Seven electronic databases (PubMed, Embase, the Cochrane Library, Web of Science, CINAHL, LiLACS, and PsycINFO) were searched for publications from 1970 up to November 2013 (updated to January 31, 2014) Anzahl eingeschlossene Studien/Patienten (Gesamt): 8 RCTs (total n = 4422) of seven different types and different dosages of atypical antipsychotics and a placebo that were included in the review. Qualitätsbewertung der Studien: Cochrane risk of bias tool
	3. Ergebnisdarstellung Qualität der Studien: The overall quality of studies was rated as good, even though many reports did not provide details about randomization and allocation concealment, while none of the RCTs met the criteria for high risk of bias on the basis of question-based entries. *Hinweis*: basierend auf Bayesian network meta-analyses • All standard-dose atypical antipsychotics were significantly more efficacious than placebo in the efficacy (standardized mean differences [SMDs] ranged from -0.27 to -0.43). • There were no significant differences between these drugs. • Low-dose atypical antipsychotics were not significantly more efficacious than the placebo. • In terms of tolerability, all standard-dose atypical antipsychotics, apart from risperidone, had significantly more side-effect

	discontinuations than placebo (odds ratios [ORs] ranged from 2.72 to 6.40). • In terms of acceptability, only quetiapine (mean 250–350 mg daily) had significantly more all-cause discontinuation than placebo (OR = 1.89). • In terms of quality of life/functioning, standard-dose risperidone and standard-dose aripiprazole were more beneficial than placebo (SMD = -0.38; SMD = -0.26, respectively), and standard-dose risperidone was superior to quetiapine (mean 250–350 mg daily).
	4. Fazit der Autoren: All standard-dose atypical antipsychotics for the adjunctive treatment of TRD are efficacious in reducing depressive symptoms. Risperidone and aripiprazole also showed benefits in improving the quality of life of patients. Atypical antipsychotics should be prescribed with caution due to abundant evidence of side effects. 5. Kommentare zum Review • the clinically important issue of adjunctive atypical antipsychotic therapy for preventing relapse in the medium and long term (i.e. ≥6 months) is not addressed
Papadimitro-poulou K et al., 2017 [29]. Comparative efficacy and tolerability of pharmacological and somatic interventions in adult patients with treatment-resistant depression: a systematic review and network meta-analysis	**1. Fragestellung** The current study compared the relative efficacy and tolerability of pharmacological and somatic TRD interventions by means of a Bayesian network meta-analysis.
	2. Methodik **Population:** Adult MDD patients who failed to respond to ≥2 antidepressant treatment regimens prescribed at adequate dose and duration **Intervention**: SSRIs, SNRIs, TCAs, tetracyclic antidepressants (TeCAs), MAOIs, atypical antidepressants, antipsychotics, olanzapine/fluoxetine combination (OFC), adjunctive use of lithium, triiodothyronine (T3), lamotrigine, ketamine, ECT and repetitive transcranial magnetic stimulation (rTMS). **Komparator:** Analog zu Interventionen **Endpunkte:** Disease severity change from baseline measured on the Hamilton (HAM-D) or Montgomery–Åsberg depression rating scales (MADRS) or other depression rating scales, response, remission, relapse and recurrence rates, time to response or relapse and tolerability outcomes **Recherche**: MEDLINE, MEDLINE In-Process, EMBASE,

	PsycInfo, EconLit (through OVID) and Cochrane Library databases (including CENTRAL, CDSR, CMR, DARE, HTAD, and NHS EED on 21 October 2013 with update on efficacy and safety in September 2014 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 31 RCT *(Gesamtzahl der Patienten nicht genannt)* **Qualitätsbewertung der Studien**: Cochrane Collaboration's tool for assessing risk of bias
	3. Ergebnisdarstellung **<u>Qualität der Studien:</u>** • 19 RCT investigated 13 pharmacological interventions • 12 RCTs investigating electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS). • In pharmacological interventions studies age ranged from 41 to 52 years • Mean baseline MADRS score in pharmacological studies was 29.8 (range 25.2 to 33.7) • Mean duration of the current depressive episode was 25 months (range 5.8 to 48.5) in 10 pharmacological intervention studies **Supplementary eFigure 1. Aggregate RoB assessment – Pharmacological intervention studies.**  **Supplementary eFigure 2. Aggregate RoB assessment – Somatic intervention studies**



Mean difference in change from baseline in Montgomery–Åsberg depression rating scale score at 2 and 6 weeks

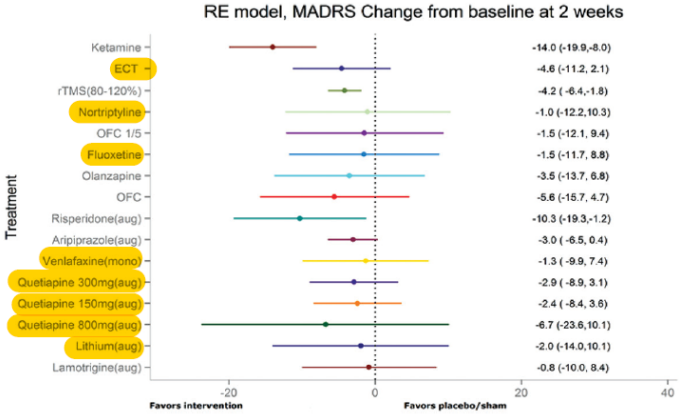


Figure 2. Network meta-analysis results – mean differences in change from baseline at 2 weeks.
RE: random effects; MADRS: Montgomery–Åsberg Depression Rating Scale; ECT: Electroconvulsive therapy; rTMS: repetitive Transcranial magnetic stimulation; OFC: Olanzapine/Fluoxetine combination; mono: monotherapy; aug: augmentation.

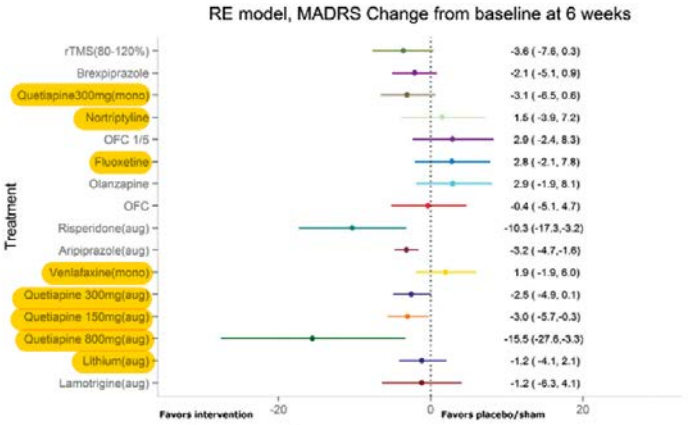


Figure 3. Network meta-analysis results – mean differences in change from baseline at 6 weeks.
RE: random effects; MADRS: Montgomery–Åsberg Depression Rating Scale; rTMS: repetitive Transcranial magnetic stimulation; OFC: Olanzapine/Fluoxetine combination; mono: monotherapy; aug: augmentation.

Response rate at 6 weeks

- At 6 weeks after baseline, augmentation with quetiapine XR 150 mg/day, XR 300 mg/day and 800 mg/day seemed more efficacious compared to placebo/sham (ORs of 2.17, 2.09, 1.36, 1.4 and 21.65), yet the 95% CrIs included 1.

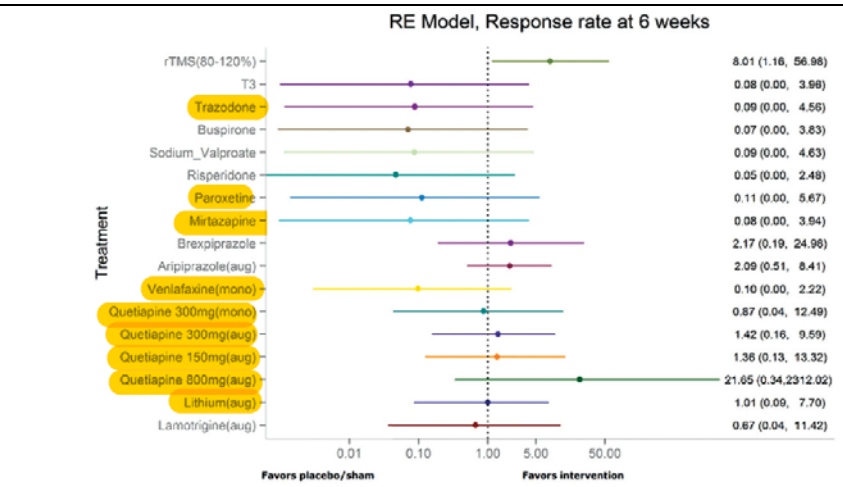
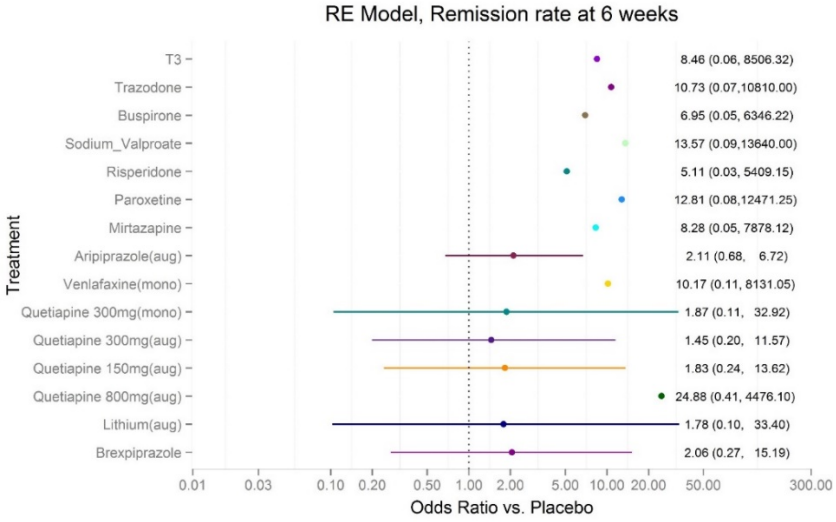


Figure 4. Network meta-analysis results – response rate at 6 weeks.
RE: random effects; rTMS: repetitive Transcranial magnetic stimulation; T3: Triiodothyronine; mono: monotherapy; aug: augmentation.

Remission at 6 weeks

- At 6 weeks after baseline, augmentation with quetiapine XR 150 mg/day, XR 300 mg/day and 800 mg/day seemed efficacious compared to placebo/sham, yet the 95% CrI included 1



Withdrawals due to adverse events (at 6 weeks)

- Quetiapine showed higher withdrawal rates due to adverse events compared to placebo/sham:

Supplementary eFigure 9. NMA results – Withdrawals due to adverse events.

	
	4. Fazit der Autoren: This Bayesian network meta-analysis is the first to compare the relative efficacy of pharmacological and somatic interventions for TRD. […] Regarding efficacy results at later timepoints, there was no clear distinction among the investigated treatments except high dose quetiapine augmentation (800 mg/day) […] which showed superior efficacy compared to the competing interventions at 4, 6 and 8 weeks analysis. This analysis revealed scarcity of long-term data (i.e. data on sustained remission) that would allow a comparative long-term efficacy assessment. **5. Kommentar zu Review** • Ausführliches feasability assessment vor Durchführung der Netzwerk-MA. Zugrundeliegende Annahmen beschrieben sowie Konsistenz und Konvergenz untersucht. *"This study was conducted by Mapi on behalf of Janssen Pharmaceutica NV who funded the study and the writing of this manuscript."*
Linde K et al., 2015 [20]. Comparative effectiveness of psychological treatments for depressive disorders in primary care: <u>network meta-analysis</u>	1. Fragestellung/Zielsetzung: to compare the effectiveness of psychological treatments grouped by theoretical background, intensity of contact with the health care professional, and delivery mode for depressed patients in this setting.
	2. Methodik Population: adult primary care patients suffering from prevalent or incident unipolar depressive disorders Intervention / Komparator: Comparison of psychological or combined psychological and pharmacological interventions with one another, a pharmacological intervention, usual care or placebo. <u>Hinweis</u>*: We grouped interventions according to the following dimensions: (1) theoretical background: cognitive behavioural therapy (CBT) vs. problem solving therapy (PST) vs. interpersonal therapy vs. psychodynamic therapies vs. other interventions; (2) intensity of contact with health care professional: intensively therapist-lead (with a minimum of six sessions) vs. guided self-help (with less than six sessions with the therapist) vs. no or minimal contact (with less than 90 minutes contact) interventions; and (3) face-to-face vs. remote contact interventions.* Endpunkte: response to treatment, remission, discontinuations Recherche: Medline, Embase, Cochrane Central Register

	of Controlled Trials (CENTRAL) and PsychINFO (main search June 2011, last update searches December 2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): A total of 37 studies with 7,024 patients met the inclusion criteria Qualitätsbewertung der Studien: Cochrane risk of bias tool.
	3. Ergebnisdarstellung Qualität der Studien: The overall risk of bias was considered low in 13, unclear in 11 and high in 13 trials. *Hinweis*: based on both Bayesian and frequentist methods • Among the psychological treatments investigated in at least 150 patients face-to-face cognitive behavioral therapy (CBT; OR 1.80; 95 % credible interval 1.35–2.39), face-to-face counselling and psychoeducation (1.65; 1.27–2.13), remote therapist lead CBT (1.87; 1.38–2.53), guided self-help CBT (1.68; 1.22–2.30) and no/minimal contact CBT (1.53; 1.07–2.17) were superior to usual care or placebo, but not face-to-face problem-solving therapy and face-to-face interpersonal therapy. • There were no statistical differences between psychological treatments apart from face-to-face interpersonal psychotherapy being inferior to remote therapist-lead CBT. • Remote therapist-led, guided self-help and no/minimal contact CBT had similar effects as face-to-face CBT.
	4. Fazit der Autoren: The limited available evidence precludes a sufficiently reliable assessment of the comparative effectiveness of psychological treatments in depressed primary care patients. Findings suggest that psychological interventions with a cognitive behavioral approach are promising, and primarily indirect evidence indicates that it applies also when they are delivered with a reduced number of therapist contacts or remotely 5. Kommentare zum Review • Keine Angaben bzw. separaten Auswertungen hinsichtlich der Vortherapie

Leitlinien

Bauer M et al., 2013 [1]. **World Federation of Societies of Biological Psychiatry (WFSBP)**	Fragestellung/Zielsetzung: to systematically review all available evidence pertaining to the treatment of unipolar depressive disorders, and to produce a series of practice recommendations that are clinically and scientifically meaningful based on the available evidence.
	Methodik

World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders. - Part 1: Update 2013 on the acute and continuation treatment of unipolar depressive disorders	Grundlage der Leitlinie This 2013 update of the practice guidelines for the biological treatment of unipolar depressive disorders was developed by an international Task Force of the World Federation of Societies of Biological Psychiatry (WFSBP). LoE/GoR Evidence-based classifi cation of recommendations: Each treatment was evaluated based upon the strength of evidence for its efficacy, safety, and feasibility. According to Bandelow et al. (2008) and Grunze et al. (2009), six categories of evidence (CE A to F) were used: CE A: Full evidence from controlled trials CE B: Limited positive evidence from controlled trials CE C: Evidence from uncontrolled studies or case reports/expert opinion CE D: Inconsistent results CE E : Negative evidence CE F : Lack of evidence. Recommendations were then derived from the category of evidence for effi cacy (CE) and from additional aspects such as safety, tolerability, and interaction potential and where labelled 1 to 5: RG 1: CE A evidence and good risk – benefit ratio RG 2: CE A evidence and moderate risk – benefit ratio RG 3: CE B evidence RG 4: CE C evidence RG 5: CE D evidence. In a number of clinically relevant questions – with no informative external evidence available to answer these questions – recommendations are made, referred to as “ Clinical consensus ”.
	Empfehlungen: **2.2.5 Diagnostic reassessment and optimizing antidepressant medication** WFSBP recommendation: In case of inadequate response to antidepressant treatment, assessing adherence to the current treatment regimen is recommended as a first step. (Clinical consensus)

	WFSBP recommendation: In possibly non-adherent patients (e.g., low drug plasma levels despite high doses of the antidepressant), a combination of TDM and genotyping may be informative. Such analyses can aid in identifying those individuals who are slow or rapid metabolizers of certain antidepressants. (Clinical Consensus) **2.2.8 Theoretical treatment options for the partial- and non-responding patient to initial treatment** The major types of theoretical strategies employed after reviewing correctness of diagnosis and suffi ciency of drug dosing and adherence, are: *(1) Increasing (maximizing) the dose of the initial antidepressant.* *(2) Switching to another antidepressant from a different pharmacological class (e.g., from a SSRI to a TCA or a dual-acting AD).* *(3) Switching to another antidepressant within the same pharmacological class (e.g., from a SSRI to another SSRI).* *(4) Combining two antidepressants from different classes (e.g., an SSRI or a dual-acting AD with e.g., mirtazapine).* *(5) Augmenting the antidepressant with other agents (e.g., lithium, thyroid hormone or atypical antipsychotics) to enhance antidepressant efficacy.* *(6) Combining the antidepressant with a psychotherapeutic intervention.* *(7) Combining the antidepressant with non pharmacological biological therapies (e.g., wake therapy, light therapy, ECT).* WFSBP recommendation: Switching from an SSRI to venlafaxine or tranylcypromine appears legitimate: With longer use of most antidepressants, stepdown discontinuation within a period of 1 – 4 weeks is recommended rather than abrupt discontinuation, as this may cause discontinuation symptoms. However, transition to the new antidepressant can be performed in an overlapping fashion in most cases. However, switching to or from an irreversible MAO inhibitor should be performed with caution and with a 2-week washout period between the two drugs (5 weeks when switching from fluoxetine) (LoE: CE C, RG 4 / Clinical consensus). WFSBP recommendation: Combination of an SSRI with an inhibitor of presynaptic autoreceptors (e.g., mirtazapine) is an evidence-based choice in cases where monotherapy failed. The combination of venlafaxine with mirtazapine may be accompanied by worsening side effects (LoE: CE A, RG 2). WFSBP recommendation:

	Adding lithium to ongoing antidepressant treatment is recommended in case monotherapy failed (LoE: CE A, RG 2) Lithium augmentation should be administered for 2 – 4 weeks in order to allow assessment of the patient ' s response. The recommended lithium serum target levels are 0.6 to 0.8 mmol/L. 1 In case of response, lithium augmentation should be continued for at least 12 months. (LoE: CE A, RG 2) The augmentation of antidepressants with thyroid hormones appears legitimate in cases where monotherapy failed. Thyroid hormones should be administered with caution because of potential unwanted effects. (LoE: CE B, RG 3) The augmentation of antidepressants with quetiapine or aripiprazole represents an alternative to lithium augmentation and is recommended in case monotherapy failed. Potential unwanted effects include sedation (quetiapine), weight gain (quetiapine, and to a lesser extent aripiprazole) and akathisia (aripiprazole) (LoE: CE A, RG 2). <u>2.4 Electroconvulsive therapy</u> WFSBP recommendation: Among the indications for Electroconvulsive therapy (ECT) as a first-line treatment are: severe major depression with psychotic features, severe major depression with psychomotor retardation, " true " treatment-resistant major depression, refusal of food intake or in other special situations when rapid relief from depression is required (e.g., in severe suicidality) or medication contraindicated (e.g., in pregnancy). ECT as a first-line approach may also be indicated in patients who have experienced a previous positive response to ECT, and in patients who prefer ECT for a specific reason (LoE: CE C, RG 4). <u>2.5 Psychotherapy</u> WFSBP recommendation: Psychotherapy should be considered as an initial treatment modality for patients with mild depression. Furthermore, psychotherapy is recommended in combination with antidepressants for patients with moderate to severe depression and for patients who have had only partial responses to antidepressant medications or who have had problems with adherence to antidepressants. Patient preference for antidepressant medications or psychotherapy and the availability of psychotherapy should be considered when deciding between initiating treatment with antidepressant medications or psychotherapy (LoE: CE B, RG 3)
Cleare A et al., 2015 [5].	Fragestellung/Zielsetzung: These guidelines are primarily concerned with the use of antidepressant drugs to treat the most common (unipolar) depressive disorders in adults, and do not cover

British Association for Psychopharmacology Evidence-based guidelines for treating depressive disorders with antidepressant: A revision of the 2008 British Association for Psychopharmacology guidelines	depression occurring in bipolar disorder (…).
	Methodik Grundlage der Leitlinie A consensus meeting was held under the auspices of the BAP in 2012 involving experts in the field of depression and antidepressant treatment, user representatives and medical and scientific staff from pharmaceutical companies. Presentations on key areas with an emphasis on systematic reviews and randomised controlled trials (RCTs) were made by each co-author of the guidelines, followed by discussion within the whole group about the quality of evidence and its implications. Subsequently, the main authors revised the previous literature review from 2008 where necessary to incorporate significant developments and drafted revised recommendations and their strength based on the level of evidence. This was then circulated to all participants, user groups and other interested parties for feedback which was incorporated into the final version of the guidelines. The breadth of information covered in these guidelines did not allow for a systematic review of all possible data from primary sources. Instead, each co-author was tasked with updating specific sections from the previous guidelines within their subspeciality, using major systematic reviews and RCTs from MEDLINE and EMBASE searches and from the Cochrane Database as well as cross-referencing from previous guidelines (e.g. American Psychiatric Association, 2010; Bauer et al., 2007; CANMAT, Kennedy et al., 2009; Ellis and Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Depression, 2004; National Institute for Clinical Excellence, 2009). LoE/GoR Table 1. Categories of evidence and strength of recommendation[a]. *Categories of evidence for causal relationships and treatment* I: evidence from meta-analysis of randomised controlled trials*, at least one large, good quality, randomised controlled trial* or replicated, smaller, randomised controlled trials* II: evidence from small, non-replicated, randomised controlled trials*, at least one controlled study without randomisation or evidence from at least one other type of quasi-experimental study III: evidence from non-experimental descriptive studies, such as uncontrolled, comparative, correlation and case-control studies IV: evidence from expert committee reports or opinions and/or clinical experience of respected authorities *Proposed categories of evidence for non-causal relationships* I: evidence from large representative population samples II: evidence from small, well-designed, but not necessarily representative samples III: evidence from non-representative surveys, case reports IV: evidence from expert committee reports or opinions and/or clinical experience of respected authorities *Strength of recommendation* A directly based on category I evidence B directly based on category II evidence or extrapolated[#] recommendation from category I evidence C directly based on category III evidence or extrapolated[#] recommendation from category I or II evidence D directly based on category IV evidence or extrapolated[#] recommendation from category I, II or III evidence S standard of good practice [a]developed from Shekelle et al. (1999). *Randomised controlled trials must have an appropriate control treatment arm; for primary efficacy this should include a placebo condition. [#]extrapolation may be necessary because of evidence that is only indirectly related, covers only a part or the area of practice under consideration, has methodological problems or is contradictory.
	Empfehlungen:

	NEXT-STEP TREATMENTS FOLLOWING INADEQUATE TREATMENT RESPONSE TO AN ANTIDEPRESSANT 3.1 TREATMENT FAILURE AND TREATMENT RESISTANCE • Assess the efficacy and risks of each alternative next-step treatment option against the severity and risks associated with the individual's depression, the degree of treatment resistance and past treatments that have been tried (S). • Check the adequacy of treatment including dose and non-adherence (S); increase dose to recommended therapeutic dose if only a low or marginal dose has been achieved (D). • Review diagnosis including the possibility of other medical or psychiatric diagnoses which should be treated in addition and the presence of symptoms suggesting unrecognised bipolarity, psychosis or atypical symptoms (S). The use of appropriate screening tools (e.g. MDQ or HCL for bipolarity) may be helpful (S). • Consider social factors maintaining the depression and, if present, help the patient address them if possible (S). • Continue adequately dosed antidepressants for at least 4 weeks before changing treatment for lack of efficacy (B). • Assessment after 4 weeks of adequate treatment: – if there is at least some improvement continue treatment with the same antidepressant for another 2–4 weeks (B), – if there is no trajectory of improvement undertake a next-step treatment (B); however, in patients who have failed a number of treatments consider longer trials before changing treatment (D). • Assessment after 6–8 weeks of adequate treatment: – if there is moderate or greater improvement continue the same treatment, – if there is minimal improvement undertake a next-step treatment (B); however, in patients who have failed a number of treatments consider longer trials before changing treatment (D). **3.2 NEXT-STEP DRUG TREATMENT OPTIONS** 3.2.1 Dose Increase (C) • The evidence supporting the efficacy of dose increase is limited, but it could be considered in individual patients especially if: – there are minimal side-effects (D) and/or, – there has been some improvement on the antidepressant (D) and/or, – the current antidepressant has a possible dose response (there is modest evidence for venlafaxine, escitalopram and TCAs) (C).

	3.2.2 Switching antidepressant (A) • Consider especially if: – there are troublesome or dose-limiting side effects (D) and/or, – there has been no improvement (D) – switching abruptly is generally preferable unless there is a potential drug interaction (D) in which case follow the recommended taper/washout period (S) – switch either within- or between-antidepressant class initially (B) – consider a different antidepressant class after more than one failure with a specific class (D); consider venlafaxine after more than one SSRI failure (B); in the absence of other indications, consider preferentially antidepressants with some evidence of slightly higher efficacy (i.e. clomipramine, venlafaxine (⩾150mg), escitalopram (20 mg), sertraline, amitriptyline or mirtazapine (D). 3.2.3 Augmentation/combination treatment (A) • Consider adding a second agent especially if: – there is partial/insufficient response on the current antidepressant (D) and, – there is good tolerability of current antidepressant (D), – switching antidepressant has been unsuccessful (D). • establish the safety of the proposed combination (S). • choose the combinations with the best evidence base first (S). • consider adding quetiapine (A), aripiprazole (A) or lithium (A) as first-line treatments, and risperidone(A), olanzapine (B), tri-iodothyronine (B) or mirtazapine (B) as second-line treatments, being aware that the evidence derives mainly from studies in which lithium and tri-iodothyronine were added to TCAs and the other drugs added to SSRI/SNRIs. • other additions that could be considered are bupropion (B), buspirone (B), lamotrigine (C) and tryptophan (C); and in specialist centres with careful monitoring (S) modafinil (C), stimulants (C), oestrogen in peri menopausal women (C) and testosterone in men with low testosterone levels (C). • In older people the evidence base is much smaller, but overall about 50% of patients respond to switchingor augmentation. The best evidence is for lithium augmentation (B). There is also some evidence for venlafaxine and selegiline (C). • In severely treatment resistant patients it may be appropriate to consider multiple combinations concurrently or to use other approaches with extremely limited evidence, but only in specialist centres with appropriate safeguards (D).

	3.3 NEXT-STEP PSYCHOLOGICAL TREATMENTOPTIONS • Consider adding CBT to ongoing antidepressant treatment (A). • Consider adding other psychological or behavioural treatments that have established acute treatment efficacy (D). **3.4 NEXT-STEP PHYSICAL TREATMENT OPTIONS** • Electroconvulsive therapy (ECT): – should be considered as an option for patients who have not responded to other treatments (C). (…) **4.2 TREATMENT OF RELAPSE WHILE ON CONTINUATION THERAPY** • Check the adequacy of treatment including dose and adherence (S). • Review diagnosis including the possibility of additional medical or psychiatric diagnoses which should be treated in addition (S). • Consider social factors and, where present, help the patient address them if possible (S). • Be aware that relapses may be self-limiting (S) and be cautious about frequent or too-early treatment changes (D). • Treatment options: – if antidepressants have been stopped re-start the patient on an antidepressant at adequate dose (B); if the dose had been lowered re-establish the previous dose (B), – in a patient on an adequate dose of medication with a recent-onset relapse initially consider providing support and monitoring without changing the medication dose (B), – consider increasing the dose of antidepressant, subject to the limitations described in section 3 (B), – consider other next-step treatments as in section 3 (D).
Jobst A et al., 2016 [12] **European Psychiatric Association (EPA)** European Psychiatric Association Guidance on psychotherapy in chronic depression across Europe	**Zielsetzung**: to provide a comprehensive overview of current psychotherapy for CD. The evidence of efficacy is critically reviewed and recommendations for clinical applications and research are given.
	Methodik Grundlage der Leitlinie - Systematic literature search in Medline (January 1977 to January 2015, Cochrane Library and reference lists - Methodology of studies assessed using grading scheme of the Scottish Intercollegiate Guidelines Network (SIGN) - Formal consensus process using Delphi method - Empfehlungen sind nicht direkt mit der Literatur verknüpft, Übersicht über die Evidenz wird in einem extra Abschnitt

vorangestellt

LoE / GoR:

Table 1
Grading of evidence from questionnaire surveys (quantitative studies), qualitative research (abbreviated and modified from [154]) and reviews.

	Levels of evidence [88]
1 ++	High-quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews or RCTs with a low risk of bias
1−[a]	Meta-analyses, systematic reviews or RCTs with a high risk of bias
2 ++	High-quality systematic reviews of case control or cohort studies. High-quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2−[a]	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Nonanalytic studies, e.g. case reports, case series
4	Expert opinion

[a] Studies graded with 1− or 2− should not be used as a basis for recommendations because of their high risk of bias.

Table 2
Grading of recommendations derived from reviews, quantitative studies (mainly questionnaire-based surveys) and qualitative research.

Modified from the Scottish Intercollegiate Guidelines Network (SIGN, [88]) grading of recommendations, mainly on the basis of intervention studies	
A	At least one meta-analysis, systematic review, or other study rated as I and directly applicable to the target population; or a body of evidence consisting principally of studies rated as I, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as II, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as I or II
C	A body of evidence including studies rated as II–III, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as II–III
D	Evidence level III or IV or Extrapolated evidence from studies rated as III or IV
Modified from the National Institute for Health and Care Excellence (NICE [155]) grading of recommendations	
A	At least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation (evidence levels Ia and Ib) without extrapolation
B	Well-conducted clinical studies but no randomised clinical trials on the topic of recommendation (evidence levels IIa, IIb, III); or extrapolated from level I evidence
C	Expert committee reports or opinions and/or clinical experiences of respected authorities. This grading indicates that directly applicable clinical studies of good quality are absent (evidence level IV), or with extrapolation from higher levels of evidence
GPP	Good practice point: recommended good practice based on the clinical experience of the Guidance development group and arrived at through consensus

Sonstige methodische Hinweise

Empfehlungen

Recommendation 1: choice of psychotherapy

Cognitive behavioural analysis system of psychotherapy is recommended as first-line treatment for CD (evidence level: 1++; recommendation grade: A) and interpersonal therapy is recommended as second-line treatment (evidence level: 1; recommendation grade: B). [78, 81]

Cognitive-behavioural therapy is recommended as third-line treatment (evidence level: 2+, recommendation grade: C).

The EPA Guidance Group recommends psychodynamic and psychoanalytic treatment as a third-line treatment on the basis of studies mixing CD and episodic MDD as well as on clinical experiences of respected experts in the field (evidence level: 3–4; recommendation grade: D). Problem-solving therapy, schema therapy, radical openness dialectical behavioural therapy and mindfulness-based cognitive therapy are also recommended as third-line treatments, because there is less empirical support for them and not enough trials have been conducted. Present studies have methodological limitations (evidence level: 2- to 1-; recommendation grade: C).

Moreover, the type of psychotherapy should be individually chosen in consideration of early versus late onset, type of depression, number of episodes, early trauma, symptom severity, patient preference and comorbid personality disorder (evidence level: 4;

	recommendation grade: Good Practice Point [GPP]). Referenzen: [78] Spijker J, van Straten A, Bockting CL, Meeuwissen JA, van Balkom AJ. Psychotherapy, antidepressants, and their combination for chronic major depressive disorder: a systematic review. Can J Psychiatry 2013;58:386–92. [81] Kriston L, von Wolff A, Westphal A, Holzel LP, Harter M. Efficacy and acceptability of acute treatments for persistent depressive disorder: A network meta-analysis. Depress Anxiety 2014. Recommendation 2: psychotherapy or pharmacotherapy? The EPA Guidance Group on CD considers both psychotherapy and pharmacotherapy to be effective in CD (psychotherapy of short duration is less effective in pure dysthymia) and recommends both approaches (evidence level: 1+; recommendation grade: A). Combined treatment with psychotherapy and pharmacotherapy has been reported to be superior to psychotherapy or pharmacotherapy alone (evidence level: 1+; recommendation grade: A) and should therefore be the first choice. The only exception is pure dysthymia, where the current evidence does not support an advantage of combined treatment. Pharmacotherapy should be individually chosen in consideration of anxiety levels, sleep problems and obsessive-compulsive symptoms. If a patient prefers monotherapy, the EPA Guidance Group recommends pharmacotherapy or psychotherapy to the same degree (evidence level: 1+, recommendation grade: A). Recommendation 3: personalized treatment The EPA Guidance Group recommends a personalized approach based on the patient's preferences and needs, e.g. pharmacotherapy or psychotherapy, group or individual psychotherapy, in- or outpatient treatment (evidence level: 4; recommendation grade: GPP).
The Canadian Network for Mood and Anxiety Treatments (CANMAT), 2016 [15,18,27,30] Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder:	**Fragestellung/Zielsetzung**: The scope of the guidelines remains the management of adults with unipolar MDD with an identified target audience of community-based psychiatrists and mental health professionals. **Methodik** Grundlage der Leitlinie … we chose a clinically useful method that balances systematic evidence review with consensus expert opinion by experienced clinicians. Expert panels were established for each of the 6 sections. Members represented content experts from the fields of psychiatry, pharmacy, and psychology. Systematische Literaturrecherche: January 1, 2009, and December 31, 2015, in electronic databases (including OVID Medline, PsycInfo, and EMBASE). For each of the questions, a systematic literature search was conducted by research staff experienced in

- Introduction and Methods - Section 2. Psychological Treatments - Section 3. Pharmacological Treatments - Section 4. Neurostimulation Treatments	systematic reviews with medical librarian consultation as needed. The evidence was summarized using evidence tables based on modified Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for meta-analyses and on Consolidated Standards of Reporting Trials (CONSORT) for RCTs. LoE/GoR The evidence was graded using level of evidence criteria from the previous guidelines1 (Table 1; siehe unten), supplemented by modified ratings from Grading of Recommendations Assessment, Development, and Evaluation (GRADE). **Table 1.** Canadian Network for Mood and Anxiety Treatments (CANMAT) Criteria for Level of Evidence. Level of Evidence[a] — Criteria 1 — Meta-analysis with narrow confidence intervals and/or 2 or more randomized controlled trials (RCTs) with adequate sample size, preferably placebo controlled 2 — Meta-analysis with wide confidence intervals and/or 1 or more RCTs with adequate sample size 3 — Small-sample RCTs *or* nonrandomized, controlled prospective studies *or* case series *or* high-quality retrospective studies 4 — Expert opinion/consensus [a]Note that Level 1 and 2 Evidence refers specifically to treatment studies in which randomized comparisons are available. Recommendations involving epidemiological or risk factors primarily arise from observational studies, and hence the highest level of evidence is usually Level 3. Higher order recommendations (e.g., principles of care) reflect higher level judgment of the strength of evidence from various data sources and therefore are primarily Level 4 Evidence. **Sonstige methodische Hinweise:** The recommendations were then expressed as lines of treatment, in which both the evidence base and clinical support were used to determine first-, second-, and third-line treatments (Table 2, siehe unten). **Table 2.** Canadian Network for Mood and Anxiety Treatments (CANMAT) Criteria for Line of Treatment. Line of Treatment — Criteria First line — Level 1 or Level 2 Evidence, plus clinical support[a] Second line — Level 3 Evidence or higher, plus clinical support[a] Third line — Level 4 Evidence or higher, plus clinical support[a] [a]Clinical support refers to application of expert opinion of the CANMAT committees to ensure that evidence-supported interventions are feasible and relevant to clinical practice. Therefore, treatments with higher levels of evidence may be downgraded to lower lines of treatment due to clinical issues such as side effects or safety profile.
	Empfehlungen

Pharmacological treatment:

Table 11. Recommendations for Adjunctive Medications for Nonresponse or Partial Response to an Antidepressant.

Recommendation	Adjunctive Agent	Level of Evidence	Dosing
First line	Aripiprazole	Level 1	2-15 mg
	Quetiapine	Level 1	150-300 mg
	Risperidone	Level 1	1-3 mg
Second line	Brexpiprazole[a]	Level 1	1-3 mg
	Bupropion	Level 2	150-300 mg
	Lithium	Level 2	600-1200 mg (therapeutic serum levels)
	Mirtazapine/mianserin	Level 2	30-60 mg
	Modafinil	Level 2	100-400 mg
	Olanzapine	Level 1	2.5-10 mg
	Triiodothyronine	Level 2	25-50 mcg
Third line	Other antidepressants	Level 3	Various
	Other stimulants (methylphenidate, lisdexamfetamine, etc.)	Level 3	Various
	TCAs (e.g., desipramine)	Level 2	Various
	Ziprasidone	Level 3	20-80 mg bid
Experimental	Ketamine	Level 1	0.5 mg/kg, single intravenous dose[b]
Not recommended	Pindolol	Level 1 (lack of efficacy)	Not applicable

TCA, tricyclic antidepressant.
[a]Newly approved since the 2009 Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines.
[b]For acute treatment.

Psychological treatment:

Table 5. Recommendations for Psychological Treatments for Acute and Maintenance Treatment of Major Depressive Disorder.

	Acute Treatment	Maintenance Treatment (Relapse Prevention)
Cognitive-behavioural therapy (CBT)	First line (Level 1)	First line (Level 1)
Interpersonal therapy (IPT)	First line (Level 1)	Second line (Level 2)
Behavioural activation (BA)	First line (Level 1)	Second line (Level 2)
Mindfulness-based cognitive therapy (MBCT)	Second line (Level 2)	First line (Level 1)
Cognitive-behavioural analysis system of psychotherapy (CBASP)	Second line (Level 2)	Second line (Level 2)
Problem-solving therapy (PST)	Second line (Level 2)	Insufficient evidence
Short-term psychodynamic psychotherapy (STPP)	Second line (Level 2)	Insufficient evidence
Telephone-delivered CBT and IPT	Second line (Level 2)	Insufficient evidence
Internet- and computer-assisted therapy	Second line (Level 2)	Insufficient evidence
Long-term psychodynamic psychotherapy (PDT)	Third line (Level 3)	Third line (Level 3)
Acceptance and commitment therapy (ACT)	Third line (Level 3)	Insufficient evidence
Videoconferenced psychotherapy	Third line (Level 3)	Insufficient evidence
Motivational interviewing (MI)	Third line (Level 4)	Insufficient evidence

(…) CBT is also effective for people with treatment-resistant depression (i.e., those who did not respond to at least 2 adequate antidepressant trials). An RCT of 469 primary care patients with depression with poor response to medication found CBT improved response and remission, with sustained effects at 3-year follow-up.89 In summary, CBT has Level 1 Evidence of efficacy and continues to be recommended as a first-line treatment for acute

	treatment of MDD. *<u>Reference</u>: Wiles N, Thomas L, Abel A, et al. Cognitive behavioural therapy as an adjunct to pharmacotherapy for primary care based patients with treatment resistant depression: results of the CoBalT randomised controlled trial. Lancet. 2013;381: 375-384.*
The Management of Major Depressive Disorder Working Group, 2016 [23]. **Department of Veterans Affairs Department of Defense** VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF MAJOR DEPRESSIVE DISORDER Version 3.0 – 2016	**Fragestellung/Zielsetzung:** to assist providers in managing patients with MDD. The patient population of interest for this CPG includes adults who are eligible for care in the VHA and DoD healthcare delivery system. It includes Veterans as well as deployed and non-deployed active duty Service Members.
	Methodik Grundlage der Leitlinie - Update to the 2009 MDD guideline - Systematische Literaturrecherche in mehreren Datenbanken im Zeitraum 2006 bis Januar bzw. April 2015 - Face-to-face meeting: o Develop and draft the clinical recommendations for the guideline o Assign a grade for recommendation (Each recommendation was graded by assessing the quality of the overall evidence base, the associated benefits and harms, the variation in values and preferences, and other implications of the recommendation.) o Konsensusprozess nicht beschrieben - Review of former recommendations not included in the systematic review and without an updated literature review - A set of recommendation categories was adapted from those used by the National Institute for Health and Care Excellence (NICE, UK) - Empfehlungen sind nicht direkt mit der Literatur verknüpft, Evidenz für jede Empfehlung wird separat diskutiert LoE / GoR - GRADE methodology to assess the quality of the evidence base and assign a grade for the strength for each recommendation. - Keine Angabe zum LoE
	Empfehlungen:

#	Recommendation	Strength*	Category†
8.	As first-line treatment for uncomplicated mild to moderate MDD (see Recommendation 17 for complex cases), we recommend offering one of the following treatments based on patient preference, safety/side effect profile, history of prior response to a specific medication, family history of response to a medication, concurrent medical illnesses, concurrently prescribed medications, cost of medication and provider training/competence: ▪ Evidence-based psychotherapy: • Acceptance and commitment therapy (ACT) • Behavioral therapy/behavioral activation (BT/BA) • Cognitive behavioral therapy (CBT) • Interpersonal therapy (IPT) • Mindfulness-based cognitive therapy (MBCT) • Problem-solving therapy (PST) ▪ Evidence-based pharmacotherapy: • Selective serotonin reuptake inhibitor (except fluvoxamine) (SSRIs) • Serotonin–norepinephrine reuptake inhibitor (SNRIs) • Mirtazapine • Bupropion ▪ The evidence does not support recommending a specific evidence-based psychotherapy or pharmacotherapy over another.	Strong For	Reviewed, New-replaced
9.	In patients who have demonstrated partial or no response to initial pharmacotherapy monotherapy (maximized) after a minimum of four to six weeks of treatment, we recommend switching to another monotherapy (medication or psychotherapy) or augmenting with a second medication or psychotherapy.	Strong For	Reviewed, New-replaced
10.	For patients who select psychotherapy as a treatment option, we suggest offering individual or group format based on patient preference.	Weak For	Reviewed, New-replaced
11.	For patients with mild to moderate MDD, we recommend offering computer-based cognitive behavioral therapy (CCBT) either as an adjunctive intervention or, based on patient preference, as a first-line treatment.	Strong For	Reviewed, Amended
12.	For patients with mild to moderate MDD who decline pharmacotherapy and who decline or cannot access first-line evidence-based psychotherapies, we suggest offering non-directive supportive therapy or short-term psychodynamic psychotherapy.	Weak For	Reviewed, New-replaced
b. Treatment of Severe, Chronic or Recurrent MDD (Complex)			
13.	We suggest offering a combination of pharmacotherapy and evidence-based psychotherapy for the treatment of patients with MDD during a new episode of care when the MDD is characterized by any of the following: ▪ Severe symptoms (i.e., PHQ-9 >20) ▪ Chronic (duration greater than two years) ▪ Recurrent (with three or more episodes)	Weak For	Reviewed, New-replaced
d. Continuation and Maintenance Treatments (All Severities and Complexities of MDD)			
15.	In patients with MDD who achieve remission with antidepressant medication, we recommend continuation of antidepressants at the therapeutic dose for at least six months to decrease risk of relapse.	Strong For	Reviewed, New-replaced
16.	In patients at high risk for recurrent depressive episodes (see Discussion) and who are treated with pharmacotherapy, we recommend offering maintenance pharmacotherapy for at least 12 months and possibly indefinitely.	Strong For	Reviewed, New-replaced
17.	For patients at high risk for relapse (e.g., two or more prior episodes, unstable remission status), we recommend offering a course of cognitive behavioral therapy (CBT), interpersonal therapy (IPT) or mindfulness-based cognitive therapy (MBCT) during the continuation phase of treatment (after remission is achieved) to reduce the risk of subsequent relapse/recurrence. ▪ The evidence does not support recommending a specific evidence-based psychotherapy over another.	Strong For	Reviewed, Amended
b. Other Considerations for the Treatment of Severe, Chronic or Recurrent MDD (Complex)			
22.	For patients with treatment-resistant MDD who had at least two adequate pharmacotherapy trials, we recommend offering monoamine oxidase inhibitors (MAOIs) or tricyclic antidepressants (TCAs) along with patient education about safety and side effect profiles of these medications.	Strong For	Reviewed, New-replaced
23.	Given the limited information on ketamine's safety and duration of effect, we recommend against the use of ketamine to treat MDD outside of a research setting.	Strong Against	Reviewed, New-added

24.	We recommend offering electroconvulsive therapy (ECT) with or without psychotherapy in patients with severe MDD and any of the following conditions: ▪ Catatonia ▪ Psychotic depression ▪ Severe suicidality ▪ A history of a good response to ECT ▪ Need for rapid, definitive treatment response on either medical or psychiatric grounds ▪ Risks of other treatments outweigh the risks of ECT (i.e., co-occurring medical conditions make ECT the safest treatment alternative) ▪ A history of a poor response to multiple antidepressants ▪ Intolerable side effects to all classes of antidepressant medications (e.g., seizures, hyponatremia, severe anxiety) ▪ Patient preference ▪ Pregnancy	Strong For	Reviewed, Amended
25.	We suggest offering treatment with repetitive transcranial magnetic stimulation (rTMS) for treatment during a major depressive episode in patients with treatment-resistant MDD.	Weak For	Reviewed, New-added
26.	We recommend against offering vagus nerve stimulation (VNS) for patients with MDD, including patients with severe treatment-resistant depression outside of a research setting.	Strong Against	Reviewed, Amended
27.	We recommend against offering deep brain stimulation (DBS) for patients with MDD outside of a research setting.	Strong Against	Reviewed, New-added

Table 6. Recommendations for Delivery of Electroconvulsive Therapy.

Recommendation	Level of Evidence
First line	
BP RUL (at 5-6 times seizure threshold)	Level I
BP BF (at 1.5-2.0 times seizure threshold)	Level I
Second line	
UBP RUL (up to 8 times seizure threshold) or UBP BF (at 1.5-2.0 times seizure threshold)	Level I
BP BT (at 1.5-2.0 times seizure threshold)	Level I
Twice-weekly ECT sessions have similar efficacy to thrice-weekly but have longer duration of treatment	Level 2
If no response to RUL after 4 to 6 treatments, switch to bilateral ECT (BT or BF)	Level 3
For maintenance pharmacotherapy post-ECT, use an antidepressant that has not been tried prior to ECT *or* nortriptyline plus lithium *or* venlafaxine plus lithium	Level 2
Maintenance use of ECT is as effective as pharmacotherapy in preventing relapse/recurrence after an acute course of ECT	Level 2

BF, bifrontal; BP, brief pulse; BT, bitemporal; ECT, electroconvulsive therapy; RUL, right unilateral; UBP, ultrabrief pulse.

Malhi GS et al., 2015 [22].

Royal Australian and New Zealand College of psychiatrists clinical practice guidelines for

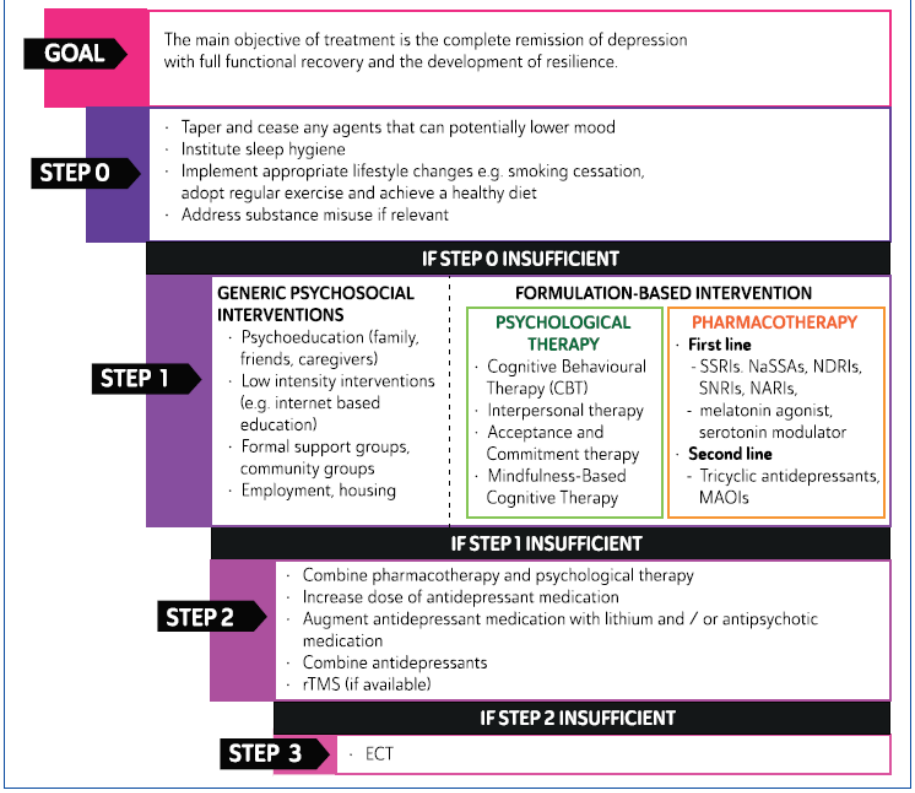
Fragestellung/Zielsetzung: To provide guidance for the management of mood disorders, based on scientific evidence supplemented by expert clinical consensus and formulate recommendations to maximise clinical salience and utility.

Methodik

Grundlage der Leitlinie

mood disorders	Articles and information sourced from search engines including PubMed and EMBASE, MEDLINE, PsycINFO and Google Scholar were supplemented by literature known to the mood disorders committee (MDC) (e.g., books, book chapters and government reports) and from published depression and bipolar disorder guidelines. The search was repeated regularly between April 2013 and October 2015. Information was reviewed and discussed by members of the MDC and findings were then formulated into consensus-based recommendations and clinical guidance. The guidelines were subjected to rigorous successive consultation and external review involving: expert and clinical advisors, the public, key stakeholders, professional bodies and specialist groups with interest in mood disorders. LoE/GoR For intervention studies, levels of evidence were assigned (see Appendix 1) and adapted from the Australian National Health and Medical Research Council (NHMRC) levels of evidence for intervention studies (NHMRC, 2009). This guideline makes two types of recommendations that reflect the reasoning used to formulate advice. First evidence-based recommendations (EBRs) were formulated when the MDC judged there to be sufficient consistent evidence from intervention studies to support a recommendation on a given topic. For each EBR, strength of evidence was rated using the NHMRC levels of evidence for intervention studies and is graded accordingly in the recommendation box (e.g., EBR I, II, III, or IV). **Table i.** Levels of evidence for intervention studies*. | Level | Design | |---|---| | I | A systematic review of level II studies | | II | A randomised controlled trial (RCT) | | III | A pseudo-randomised controlled trial (i.e. alternate allocation or some other method) A comparative study with concurrent controls: Non-randomised, experimental trial Cohort study Case-control study Interrupted time series with a control group A comparative study without concurrent controls: Historical control study Two or more single arm studies Interrupted time series without a parallel control group | | IV | A case series with either post-test or pre-test/post-test outcomes | *Adapted from: NHMRC levels of evidence for intervention studies (NHMRC, 2009).
	Empfehlungen

Figure 6. Management of major depressive disorder.



Schematic illustration of step-wise management of major depressive disorder: In Step 1 a whole host of interventions and therapies need to be considered and choice of treatment should be based on individual formulation. Note the various steps are not necessarily sequential and in some instances treatment may commence with options from Step 2 and Step 3.

Recommendation Box 1.

PSYCHOLOGICAL THERAPY FOR MDD	Grade
1.1. Psychological interventions should only be delivered by clinicians trained in the relevant evidence-based approach.	CBR
1.2. Treatment should be guided by a published manual, tailored to the individual, and should pay particular attention to establishing and maintaining the therapeutic alliance.	CBR
1.3. Patients with *mild-moderate depression* should be offered one of the evidence-based psychotherapies as first line treatment.	EBR I
1.4. Patients with *moderate-severe depression* should be offered combined pharmacotherapy and psychotherapy as first line treatment.	EBR I
1.5. Patients with *chronic depressive disorders* should be offered combined psychotherapy and pharmacotherapy as first line treatment.	EBR I

Recommendation Box 2.

ANTIDEPRESSANT THERAPY FOR MDD	Grade
2.1. An *adequate trial of antidepressant therapy for MDD* should be a minimum of three weeks at the recommended therapeutic dose using a suitable medication.	EBR III
2.2. When *commencing antidepressant therapy* clinical response and side effects should be closely monitored from the outset.	CBR

Footnote: Tolerability (side effect profile) is as important as efficacy when choosing an antidepressant.
Tricyclics, MAOIs and dual action agents may be more efficacious than newer agents in the treatment of moderate-severe depression.

Recommendation Box 3.

COMBINATION THERAPY FOR MDD	Grade
3.1. A combination of psychological and pharmacological therapy should be considered when response to either modality alone has been suboptimal or unsuccessful.	CBR

Table 13. Summary of antidepressant clinical use – acute.

Typical recommendation[a]	Antidepressant Class	Generic Name of Medication
1st line	SSRI	Citalopram, Escitalopram, Fluvoxamine, Fluoxetine, Paroxetine, Sertraline
	NARI	Reboxetine[b]
	NaSSA	Mirtazapine Mianserin
	Melatonergic agonist	Agomelatine
	NDRI	Bupropion[c]
2nd line	SNRI[d]	Desvenlafaxine, Venlafaxine,[e] Duloxetine, Milnacipran
	TCA	Amitriptyline, Clomipramine, Dothiepin, Imipramine, Nortryptiline Trimipramine Doxepin
	Serotonin Modulator*	Vortioxetine
3rd line	MAOI	Phenelzine, Tranylcypromine
	Reversible MAOI	Moclobemide
Adjunctive	SARI	Trazodone

Table 16. First- and second-line indications for ECT.

Indications for ECT	
First-line treatment	Severe melancholic depression, especially when the patient is refusing to eat/drink High risk of suicide High levels of distress Psychotic depression or catatonia Previous response, patient choice
Second-line treatment	Patients who have not responded to several trials of medication, including for example TCAs, MAOIs.

Recommendation Box 4.

ECT and rTMS FOR MDD	Grade
4.1. ECT is a safe and effective treatment for more severe presentations of depression* and should be considered first-line for psychotic depression or when an immediate response is necessary.	EBR I
4.2. Patients with non-psychotic depression may be treated with rTMS once they have failed one or more trials of standard antidepressant medications and psychological therapies.	EBR I

Footnote: *Includes major depressive episodes occurring in context of Bipolar Disorder.

Recommendation Box 5.

THE MANAGEMENT OF TREATMENT RESISTANT MDD*	Grade
5.1. The first step when faced with non-response should be to re-evaluate the formulation in particular the diagnosis.	CBR
5.2. The clinical assessment of a patient with treatment resistant depression should include a review of their treatment history, in particular their engagement with psychotherapy, and adherence to medication at the dosages prescribed. A re-evaluation of potential personality, psychiatric and medical comorbidities, and ongoing psychosocial stressors is also necessary. If the diagnosis is uncertain, or the reason for treatment non-response is not evident, then (where possible) a second opinion should be promptly sought.	CBR
5.3. In instances where a partial response has been achieved, if feasible an increase in antidepressant dose should be considered.	CBR
5.4. If after a partial response has been achieved further improvement does not occur, then, where possible, first consider augmentation and/or combination therapy prior to considering alternative strategies such as switching/ substitution.	CBR
5.5. Optimal treatment for both acute severe depression and chronic depression is a combination of pharmacotherapy and psychotherapy. The combination can consequently be considered first line for treatment resistant depression.	CBR

Footnote: If inexperienced in using medication doses above the recommended maximum, then consider seeking a second opinion. If symptoms have not significantly improved after a few weeks of treatment, re-evaluate the diagnosis.
* Also refer to Recommendation Box 6.

	Recommendation Box 6. *** ECT and rTMS IN THE MANAGEMENT OF TREATMENT RESISTANT DEPRESSION** — **Grade** 6.1. ECT is an effective therapy for medication resistant depression that should be considered after one or more unsuccessful medication trials. — EBR I 6.2. rTMS is an effective therapy that may be considered when patients have failed one or more trials of medication — EBR I 6.3. ECT is an effective therapy for medication resistant depression that may still be considered after failure of rTMS. — CBR 6.4. ECT should not be regarded a treatment of last resort and its administration should be considered on the basis of individual patient and illness factors. — EBR IV Footnote: The option of using ECT before or after rTMS is a matter for clinical judgement; the evidence supporting the effectiveness of ECT is stronger but the side effect profile is better for TMS. *Also refer to Recommendation Box 5. **Recommendation Box 7.** **MAINTENANCE TREATMENT OF MDD** — **Grade** 7.1. Patients with depression should be monitored regularly beyond the acute phase of treatment to ensure complete remission of symptoms and full functional recovery. — CBR 7.2. MBCT or CBT should be offered as a relapse prevention intervention, particularly amongst patients with recurrent depressive episodes. — EBR I 7.3. Once a satisfactory therapeutic response has been achieved, antidepressant dosage should remain the same during continuation and maintenance phases of treatment. — EBR I 7.4. Maintenance antidepressant treatment should be continued for at least six months and up to one year[a]. — CBR Notes: Once remission has been achieved, antidepressant medication confers preventive benefit. The choice of antidepressant dose is also determined by additional factors such as prior illness severity and response to treatment, comorbid disorders and medication tolerance. Footnote: a. This is particularly important if a recurrent pattern of illness has been established.
Working Group of the Clinical Practice Guideline on the Management of Depression in Adults, 2014 [36]. **THE SPANISH NHS** Clinical Practice Guideline on the Management of Depression in Adults	**Fragestellung/Zielsetzung** – Improve the healthcare given to patients with depression in the field of primary and secondary care in the Spanish National Health System. – Provide updated recommendations for the healthcare professionals involved in caring for patients with depression. – Promote rationality and effectiveness in choosing the different treatment options. – Propose a therapeutic algorithm. […]
	Methodik Grundlage der Leitlinie – Update of 2008 guideline – Working group to update the CPG, comprising two experts in methodology from the Galicia Health Technology Assessment Agency (avalia-t) and an interdisciplinary group of health professionals, composed of three psychiatrists, two clinical psychologists, a family doctor and a mental health specialist nurse – External review process – Reformulation of clinical questions using PICO format. – Systematic review of qualitative and quantitative literature – Recherche: Cochrane Library Plus, NHS Centre for Reviews and Dissemination database, TRIP), the National Guideline Clearinghouse and GuiaSalud, Medline (PubMed), EMBASE (Ovid), ISI WEB, Bibliographic Index of Health Sciences (IBECS) and the Spanish Medical Index (IME), PsycINFO from from January 2007 to February 2014 for updated questions, no time limit for new questions

– Assessment of the quality of quantitative studies with SIGN and CASP
– Formulation of recommendations based on SIGN “formal evaluation” or “reasoned judgment” criteria.

SIGN Levels of evidence and grades of recommendation

Levels of evidence	
1++	High quality meta-analyses, systematic reviews of clinical trials or high-quality clinical trials with very low risk of bias.
1+	Well-conducted meta-analyses, systematic reviews of clinical trials, or well-conducted clinical trials with little risk of bias.
1-	Meta-analyses, systematic reviews of clinical trials or clinical trials with high risk of bias.
2++	High quality systematic reviews of case control or cohort or studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.
2-	Cohort or case-control studies with a high risk of bias and a significant risk that the relationship is not causal.
3	Non-analytical studies such as case reports and case series.
4	Expert opinion.
Grades of recommendation	
A	At least one meta-analysis, systematic review or clinical trial rated as 1^{++} directly applicable to the target population of the guide; or a body of evidence consisting of studies rated as 1^{+} and showing overall consistency of results.
B	A body of evidence consisting of studies rated as 2^{++}, directly applicable to the target population of the guide and showing overall consistency of results; or evidence extrapolated from studies rated as 1^{++} or 1^{+}.
C	A body of evidence consisting of studies rated as 2^{+} directly applicable to the target population of the guide and showing overall consistency of results; or evidence extrapolated from studies rated as 2^{++}.
D	Evidence level 3 or 4; or evidence extrapolated from studies rated as 2^{+}.

Studies classified as 1^{-} and 2^{-} must not be used in the preparation of recommendations due to their high potential for bias.

The recommendations adapted from a CPG are indicated with the superscript “CPG”.

Q^{1}	Evidence taken from relevant qualitative studies of appropriate quality. This category is not considered by SIGN.
Good clinical practice	
$\surd^{2}$	Recommended practice based on clinical experience and consensus of the editorial team.

Sonstige methodische Hinweise

Evidenz- und konsensbasierte Leitlinie entsprechend deutscher S3-Klassifikation.

Empfehlungen

<u>Psychotherapeutic treatment</u>

Recommendations

√	The availability of psychotherapeutic treatment should be ensured for patients who need it.
B	In mild-moderate depression, a brief psychological treatment (such as cognitive behavioural therapy or problem-solving therapy) of 6-8 sessions over 10-12 weeks should be considered.
B	The psychological treatment of choice for moderate to severe depression is cognitive behavioural therapy or interpersonal therapy, of 16-20 sessions over 5 months.
B	Cognitive behavioural therapy should be considered for patients with inadequate response to other interventions or a prior history of relapses and/or residual symptoms.
C	Other psychological interventions should be considered when addressing comorbidity or the complexity of family or marital relationships, often associated with depression.
B	Patients with chronic and/or recurrent depression are recommended a combination of drug therapy and cognitive behavioural therapy.

Pharmacotherapy

Tricyclic antidepressants versus other antidepressants

Evidence summary

Tricyclic antidepressants versus placebo	
1+	Tricyclic antidepressants are more effective than placebo in both response and remission, but are more likely to cause side effects and early treatment dropout[13,178].
1+	When compared with placebo, tricyclic antidepressants show greater efficacy than each of the different groups of antidepressants and as a group[177].
1+	Of all tricyclic antidepressants, amitriptyline has the highest efficacy compared to placebo, followed by imipramine[177].
Tricyclic antidepressants versus other antidepressants	
1+	No clinically relevant differences between amitriptyline and other antidepressants (including SSRIs) were found after evaluating the response rate. However, patients treated with other antidepressants had fewer side effects and were less likely to leave the study[13].

1+	There were no clinically relevant differences in the response or remission rates for tricyclic antidepressants (other than amitriptyline) when compared with other antidepressants; although there were significant differences in favour of other antidepressants on reducing the probability of leaving the study early due to side effects[13].
1+	Another systematic review found no differences between tricyclic antidepressants and SSRIs, either in response rate or remission. However, SSRIs had lower dropout rates and adverse effects than tricyclics[178].

Efficacy and safety of monoamine oxidase inhibitors

Evidence summary

MAOIs versus placebo	
1+	A clinically relevant difference was observed in favour of moclobemide for both response rate and reducing depression symptoms at the end of treatment. There were no clinically relevant differences between moclobemide and placebo on reducing the likelihood of early discontinuation of treatment[13].
1+	Selegiline has shown a response rate 33% higher than placebo[177].
MAOIs versus other antidepressants	
1+	Moclobemide showed no clinically relevant differences in response or remission rate over other antidepressants (TCAs and SSRIs)[13].
1+	There was less probability of treatment drop-out with moclobemide due to the side effects of SSRIs and especially TCAs[13].

Comparison between SSRIs and other second generation antidepressants

Evidence summary

1+	Some statistically significant differences are observed in the efficacy of SSRI antidepressants when compared with each other but they are of dubious clinical relevance[170,179]. No significant differences in maintaining response or achieving remission are seen for different SSRIs (escitalopram vs paroxetine, fluoxetine vs sertraline and fluvoxamine vs sertraline)[170,179].
1+	No significant differences were observed in the efficacy of SSRIs and other second generation antidepressants (NDRI SNRI, SARI and NaSSA)[170,179].
1+	Although some studies have shown that mirtazapine could be more rapidly acting than other SSRIs (citalopram, fluoxetine, paroxetine and sertraline), its antidepressant efficacy is no greater. The response rate at 4 weeks is similar, and the NNT is 7 for an additional response in the first or second week[170,179].
1+	Comparison between different SSRIs and venlafaxine XR showed no difference in remission rates, although some secondary endpoints were favourable to venlafaxine XR[181].
1+	No differences were found in efficacy between SSRIs and duloxetine[182].
1+	For patients with major depression and a high risk of suicide, no differences were found between paroxetine and bupropion in suicidal behaviour or severity of depression; although patients with higher levels of suicidal ideation at baseline and treated with paroxetine obtained a significant improvement compared to those treated with bupropion[183].

1+	The comparison between second generation antidepressants (duloxetine vs desvenlafaxine, mirtazapine vs desvenlafaxine, mirtazapine vs trazodone, venlafaxine vs bupropion and bupropion vs trazodone) showed no significant differences in the response rate, nor for preventing relapse or recurrence between trazodone and venlafaxine[170,179].
1+	No differences were observed in response or remission rates between desvenlafaxine and duloxetine[185], nor for relapse rates between desvenlafaxine and escitalopram[186].
1+	Approximately 63% of patients treated with second generation antidepressants have mild adverse events during treatment (diarrhoea, dizziness, dry mouth, fatigue, headache, nausea, sexual dysfunction, sweating, tremors or weight gain). Overall comparisons between individual antidepressants showed no differences in the intensity of adverse events, although their frequency was different among some antidepressants[170,172,173,179].
3	An observational study conducted in Spain found 59% of patients treated with second generation antidepressants had sexual dysfunction[170,179].
1+	Bupropion leads to lower rates of sexual dysfunction than escitalopram, fluoxetine, paroxetine and sertraline; while rates of paroxetine are higher than other second generation antidepressants[170,179].
1+	SSRIs and second generation antidepressants do not appear to be associated with an increased risk of suicide in adults[170,172,179].

Reboxetine versus other antidepressants

Evidence summary

Reboxitine versus placebo	
1+	A clinically relevant difference was found in 3 RCTs for reboxetine over placebo for response rate with some evidence only regarding remission rate[13].
1+	A subsequent systematic review of published and unpublished RCTs found no statistically significant differences between reboxetine and placebo for response or remission rate at the end of treatment[189,190].
1+	Reboxetine was associated with higher rates of adverse effects and drop-outs than placebo[189,190].
Reboxitine versus other antidepressants	
1+	No clinically relevant differences were found in 3 RCTs between reboxetine and other antidepressants for response or remission rates or in reducing depression symptoms at the end of treatment[13].
1+	Reboxetine had a remission rate significantly lower than SSRIs in 1 systematic review[189,190].
1+	A meta-analysis found that reboxetine was significantly less effective than 11 antidepressants[191], and 1 RCT showed that treatment with reboxetine did not confer any advantage over in patients with major depression in primary care[192].
1+	No differences in adverse events were found between reboxetine and other antidepressants, such as SSRIs[13,189,190], and it was worse tolerated than bupropion, citalopram, escitalopram, fluoxetine and sertraline individually[191].

Efficacy and safety of agomelatine

Evidence summary

1+	Agomelatine is more effective than placebo in the treatment of moderate to severe major depression, both in the acute phase[199] and for relapse prevention[209].
1+	Younger patients and those with a greater number of previous episodes and of a shorter duration respond more favourably to agomelatine than placebo[199].
1+	Agomelatine is more efficacious than other active comparators (paroxetine, venlafaxine, venlafaxine XR, sertraline, fluoxetine and escitalopram)[199,214], although the size of the effect brings the clinical relevance of these results into question[199].
1+	Agomelatine was more efficacious than venlafaxine in reducing anhedonia in 1 RCT, though not in reducing the symptoms of depression or anxiety[216].
3	A prospective observational study of 3,317 patients diagnosed with major depression and treated with agomelatine showed a decrease in the MADRS scale score of 18.3 points at 12 weeks, with a 65.8% response rate and 54.8% remission. About 80% of patients improved in difficulty of falling asleep and nocturnal awakenings, as well as daytime sleepiness[217].
1+	The most common adverse effects of agomelatine are present in less than 15% of patients and are slightly higher with a dose of 50 mg/day than 25 mg/day[218].
1+	The losses due to adverse effects in clinical trials were significantly lower in the groups treated with agomelatine than with the comparators[199,214].
1+	Agomelatine, bupropion, mirtazapine, moclobemide and transdermal selegiline show similar percentages of sexual dysfunction to placebo[173].
1+	A RCT that evaluated the effect of agomelatine found no significant differences with venlafaxine for sexual function[212].
1+	Agomelatine was more efficacious than venlafaxine, sertraline and escitalopram for different sleep-related parameters[211,213,215].
1+	In a study evaluating discontinuation symptoms for agomelatine and paroxetine, none were found in either the first or second week after discontinuation with agomelatine, while there were discontinuation symptoms in the first week for a group receiving paroxetine[219].
1+	Patients treated with agomelatine had a risk of increased transaminase (1.4% at doses of 50 mg/day and 1% with 25 mg/day). Severe hepatic reactions (10 times the normal limit) were reported less frequently[218].
4	The AEMPS recommended liver function monitoring at 3, 6, 12 and 24 weeks, and periodically thereafter, after starting agomelatine treatment, when the dose of agomelatine is increased and when clinically indicated[220].

Role of benzodiazepines in the treatment of depression

Evidence summary

4	Benzodiazepines can produce improvement in some symptoms of depression. However, they should not be used for more than 2-3 weeks to prevent the development of dependence[13].

Antidepressant withdrawal symptoms

3	The NICE CPG recommends maintaining treatment with antidepressant medication for at least 6 months after remission of the episode. The need for more than 6 months maintenance would depend on the number of previous episodes of depression, the presence of residual symptoms or the occurrence of comorbidity or psychosocial difficulties[13].
3	Other CPGs recommend maintaining treatment with antidepressant drugs 12 months after remission of the episode, and considering long-term (a minimum of 2 years) antidepressant treatment for those patients with risk factors[225].
1+	The maintenance dose should be the same as that given during improvement, as it has been observed that patients who reduce the dose have higher relapse rates than those who continue with the same dosage[226].
3	A study conducted in Spain found that only 22% of patients were able to maintain treatment during the recommended period (a minimum of 6 months); meanwhile, 78% discontinued treatment before reaching that deadline, with the highest percentage of abandonment occurring during the first 4 months. It was also observed that men were more likely than women to abandon the drug treatment early; with 50% of men reportedly stopping medication after 2 months and 50% of women after 3 months[228].
4	Antidepressant treatment should be stopped by reducing the dose gradually; usually over a period of 4 weeks, although some people need longer periods, particularly with drugs with a short half-life such as paroxetine or venlafaxine. Because of its long half-life, a gradual reduction would not be necessary with fluoxetine[13].

Recommendations

√	Before starting antidepressant treatment, patients must be adequately informed of the expected benefits, side effects and possible delay in the therapeutic effect.
A	The initial selection of drug therapy should be based mainly on the side effect profile and tolerability, safety and pharmacological properties, as well as other factors such as previous response to treatment, cost and patient preferences.
A	SSRIs are antidepressants with the most evidence and better risk/benefit ratio, and should be considered as the first choice of treatment.

√	All patients with moderate depression treated with drugs should be re-assessed within 15 days of the treatment start, and within 8 days in the case of severe depression.
D[GPC]	Benzodiazepine treatment may be considered for patients with anxiety, insomnia and/or agitation, although they should not be used for longer than 2-3 weeks to prevent the development of dependence.
√	Patients undergoing drug therapy must be closely monitored, at least for the first 4 weeks.
D	Antidepressant treatment should be maintained for at least 6 months after remission of the episode, and aspects such as previous episodes, comorbidity and the presence of other risk factors should be evaluated before deciding on withdrawal of treatment.
A	It is recommended that maintenance treatment be performed with the same dose at which the response was achieved.
D[GPC]	To avoid withdrawal symptoms, the antidepressant treatment dose should be reduced gradually, usually over a period of 4 weeks; particularly for drugs with short half-lives like paroxetine or venlafaxine.
D[GPC]	If withdrawal symptoms occur, a diagnostic confirmation should be performed and, if the symptoms are significant, reintroducing the original antidepressant at effective doses should be considered (or the use of another antidepressant in the same class with a long half-life) and the dose gradually reduced.
Q	When drug treatment is prescribed, the patient's perception should be explored and a positive attitude will be favoured. In addition, adequate monitoring for side effects, as well as evolution of the symptoms and functional capacity, should be performed. Moreover, after obtaining patient authorisation, any doubts the family has about the treatment must be clarified to gain their support.

Psychotherapeutic strategies in resistant depression

Recommendations

B	A combined therapy of cognitive behavioural therapy and antidepressant pharmacotherapy is recommended for patients with resistant depression.

Pharmacological strategies in resistant depression

Recommendations

√	The following is recommended for patients who do not improve with initial antidepressant treatment for depression: - Review of diagnosis. - Verify compliance with taking the appropriate dosage and treatment time. - Assess the existence of disease awareness, motivation to change and possible comorbidity
√	The following is recommended for patients with a partial response after the 3rd or 4th week: - Wait for clinical evolution until the 8th week. - Increase the drug dose to the maximum therapeutic dose.
B	If the patient does not respond by the 3rd or 4th week of treatment, any of the following strategies could be attempted: - Change of antidepressant to another in the same or a different family. - Combination of antidepressants. - Enhancement with lithium or antipsychotics.
C	When the strategy is changing the antidepressant, a different SSRI or another second-generation antidepressant should initially be evaluated. If there is no response, an antidepressant with greater side effects, such as a tricyclic or MAOI, could be assessed
C	The combination of SSRI and mianserin or mirtazapine may be a recommendable option, bearing in mind the possibility of adverse effects.
C	Enhancement with lithium or antipsychotics, such as olanzapine, quetiapine, aripiprazole or risperidone may also be a strategy to consider, bearing in mind the possibility of greater adverse effects.
D[GPC]	When enhancement or a drug combination is used: - Be aware that these strategies usually increase adverse effects. - Select those drugs for which there is information on safety in combined use. - Document the rationale for the strategy. - Monitor carefully for adverse effects.
√	There are insufficient data to recommend enhancement with carbamazepine, lamotrigine, topiramate, valproate, pindolol, thyroid hormones, zinc or benzodiazepines.

Electroconvulsive therapy

Recommendations

A	Electroconvulsive therapy should be considered a therapeutic option in patients with severe depression; mainly if there is a need for a rapid response due to high suicidal intent, severe physical damage or when other treatments have failed.
√	ECT should always be given by experienced professionals, following a physical and psychiatric assessment and in a hospital setting; and informed consent is essential.
Q	The decision to use ECT should be made jointly with the patient and/or family, by taking into account factors such as diagnosis, type and severity of symptoms, medical history, risk/benefit ratio, alternative therapies and patient preference.
Q	Should ECT be required, it is recommended to place special emphasis on providing all the necessary information, focusing on the purpose of the procedure, the side effects and a treatment plan.

National Institute for Health & Clinical Excellence, 2010	**Fragestellung/Zielsetzung** The guideline makes recommendations for the treatment and management of depression. It aims to:

[28]. **Last updated: April 2016** DEPRESSION THE TREATMENT AND MANAGEMENT OF DEPRESSION IN ADULTS (UPDATED EDITION)	[…] ● evaluate the role of specific psychological and psychosocial interventions in the treatment of depression ● evaluate the role of specific pharmacological interventions in the treatment of depression […] ● integrate the above to provide best-practice advice on the care of people with depression and their family and carers […]
	Methodik Grundlage der Leitlinie - Update of 2007 guideline with full evidence update 2012 - Repräsentative Leitliniengruppe formulierte klinische Fragestellungen als Basis für Literaturrecherchen - Informale Konsensusmethoden zur Formulierung von Empfehlungen, sofern Evidenz nicht ausreichend - Update-Recherche: Systematische Recherche (bis 2011) in CINAHL, Cochrane Database of Systematic Reviews – Cochrane Library, Embase, MEDLINE, PsycINFO, AMED (for St John's Wort only) - Durchführung von Metaanalysen wenn angebracht - Erstellung von GRADE Evidenzprofilen LoE The quality of the evidence was based on the quality assessment components (study design, limitations to study quality, consistency, directness and any other considerations) and graded using the following definitions: ● High = further research is very unlikely to change our confidence in the estimate of the effect ● Moderate = further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate ● Low = further research is very likely to have an important impact on our confidence in the estimate of the effect and is likely to change the estimate ● Very low = any estimate of effect is very uncertain. **Sonstige methodische Hinweise** Evidenzbasierte Leitlinie entsprechend deutscher S2e-Klassifikation. Evidenzprofil und Forest Plots nur verfügbar auf CD. Empfehlungen und Evidenz in separaten Kapiteln dargestellt.

	Empfehlungen **PHARMACOLOGICAL 'NEXT-STEP' TREATMENT FOR DEPRESSION THAT HAS NOT ADEQUATELY RESPONDED TO TREATMENT** 12.3.16.1 When reviewing drug treatment for a person with depression whose symptoms have not adequately responded to initial pharmacological interventions: • check adherence to, and side effects from, initial treatment • increase the frequency of appointments using outcome monitoring with a validated outcome measure • be aware that using a single antidepressant rather than combination medication or augmentation (see 12.3.16.9 to 12.3.16.13) is usually associated with a lower side-effect burden • consider reintroducing previous treatments that have been inadequately delivered or adhered to, including increasing the dose • consider switching to an alternative antidepressant. The evidence for an advantage of switching to another antidepressant over continuing treatment with the existing antidepressant is not strong. In addition, there is insufficient robust evidence about which antidepressant to switch to. Choice should therefore be guided by side effects and possible interactions during the period of the switch. 12.3.16.2 When switching to another antidepressant, be aware that the evidence for the relative advantage of switching either within or between classes is weak. Consider switching to: • initially a different SSRI or a better tolerated newer-generation antidepressant • subsequently an antidepressant of a different pharmacological class that may be less well tolerated, for example venlafaxine, a TCA or an MAOI. 12.3.16.3 Do not switch to, or start, dosulepin because evidence supporting its tolerability relative to other antidepressants is outweighed by the increased cardiac risk and toxicity in overdose. 12.3.16.4 When switching to another antidepressant, which can normally be achieved within 1 week when switching from drugs with a short half-life, consider the potential for interactions in determining the choice of new drug and the nature and duration of the transition. Exercise particular caution when switching: • from fluoxetine to other antidepressants, because fluoxetine has a long half-life (approximately 1 week) • from fluoxetine or paroxetine to a TCA, because both of these drugs inhibit the metabolism of TCAs; a lower starting dose of the TCA will be required, particularly if switching from fluoxetine because of its long half-life • to a new serotonergic antidepressant or MAOI, because of the risk of serotonin syndrome201 • from a non-reversible MAOI: a 2-week washout period is required (other antidepressants should not be prescribed

	routinely during this period). 12.3.16.5 For a person whose depression has failed to respond to various strategies for augmentation and combination treatments, consider referral to a practitioner with a specialist interest in treating depression, or to a specialist service. 12.3.16.9 When using combinations of medications (which should only normally be started in primary care in consultation with a consultant psychiatrist): • select medications that are known to be safe when used together • be aware of the increased side-effect burden this usually causes • discuss the rationale for any combination with the person with depression, follow GMC guidance if off-label medication is prescribed, and monitor carefully for adverse effects • be familiar with primary evidence and consider obtaining a second opinion when using unusual combinations, the evidence for the efficacy of a chosen strategy is limited or the risk–benefit ratio is unclear • document the rationale for the chosen combination. 12.3.16.10 If a person with depression is informed about, and prepared to tolerate, the increased side-effect burden, consider combining or augmenting an antidepressant with: • lithium or • an antipsychotic such as aripiprazole, olanzapine, quetiapine or risperidone or • another antidepressant such as mirtazapine or mianserin. 12.3.16.13 The following strategies should not be used routinely: • augmentation of an antidepressant with a benzodiazepine for more than 2 weeks as there is a risk of dependence • augmentation of an antidepressant with buspirone, carbamazepine, lamotrigine or valproate as there is insufficient evidence for their use • augmentation of an antidepressant with pindolol or thyroid hormones as there is inconsistent evidence of effectiveness. <u>Electroconvulsive therapy (ECT)</u> 12.4.9.1 Consider ECT for acute treatment of severe depression that is life threatening and when a rapid response is required, or when other treatments have failed. 12.4.9.2 Do not use ECT routinely for people with moderate depression but consider it if their depression has not responded to multiple drug treatments and psychological treatment. 12.4.9.3 For people whose depression has not responded well to a previous course of ECT, consider a repeat trial of ECT only after: • reviewing the adequacy of the previous treatment course and • considering all other options and

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- discussing the risks and benefits with the person and/or, where appropriate, their advocate or carer.

12.4.9.10 If a person's depression has responded to a course of ECT, antidepressant medication should be started or continued to prevent relapse. Consider lithium augmentation of antidepressants.
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S3-Leitlinie/Nationale Versorgungs-Leitlinie Unipolare Depression Langfassung (2. Auflage)</td><td>

Fragestellung/Zielsetzung: Empfehlungen zur Erkennung, Diagnostik und Behandlung von Depressionen in Deutschland

Methodik

Grundlage der Leitlinie

Niveau: S3-Leitlinie

Gültigkeit: Die 2. Auflage der NVL/S3-Leitlinie Unipolare Depression wurde am 16. November 2015 durch die Träger des NVL-Programms verabschiedet und ist bis zur nächsten Überarbeitung bzw. spätestens bis November 2020 gültig.

LoE/GoR

Tabelle 1: Evidenzebenen

Ia	Evidenz aus einer Metaanalyse von mindestens drei randomisiert-kontrollierten Studien (randomized controlled trials, RCTs).
Ib	Evidenz aus mindestens einer randomisiert-kontrollierten Studie oder einer Metaanalyse von weniger als drei RCTs.
IIa	Evidenz aus zumindest einer methodisch gut kontrollierten Studie ohne Randomisierung.
IIb	Evidenz aus zumindest einer methodisch guten, quasi-experimentellen deskriptiven Studie.
III	Evidenz aus methodisch guten, nichtexperimentellen Beobachtungsstudien, wie z. B. Vergleichsstudien, Korrelationsstudien und Fallstudien.
IV	Evidenz aus Berichten von Expertenkomitees oder Expertenmeinung und/oder klinische Erfahrung anerkannter Autoritäten.

Tabelle 2: Grade der Empfehlung

A	**„Soll"-Empfehlung:** Zumindest eine randomisierte kontrollierte Studie von insgesamt guter Qualität und Konsistenz, die sich direkt auf die jeweilige Empfehlung bezieht und nicht extrapoliert wurde (Evidenzebenen Ia und Ib).
B	**„Sollte"-Empfehlung:** Gut durchgeführte klinische Studien, aber keine randomisierten klinischen Studien, mit direktem Bezug zur Empfehlung (Evidenzebenen II oder III) oder Extrapolation von Evidenzebene I, falls der Bezug zur spezifischen Fragestellung fehlt.
0	**„Kann"-Empfehlung:** Berichte von Expertenkreisen oder Expertenmeinung und/oder klinische Erfahrung anerkannter Autoritäten (Evidenzkategorie IV) oder Extrapolation von Evidenzebene IIa, IIb oder III. Diese Einstufung zeigt an, dass direkt anwendbare klinische Studien von guter Qualität nicht vorhanden oder nicht verfügbar waren.
KKP*	**„Klinischer Konsenspunkt":** Empfohlen als gute klinische Praxis („Good Clinical Practice Point") im Konsens und aufgrund der klinischen Erfahrung der Mitglieder der Leitliniengruppe als ein Standard in der Behandlung, bei dem keine experimentelle wissenschaftliche Erforschung möglich oder angestrebt ist.

Tabelle 3: Überleitung der Evidenzgrade der S3-Leitlinie in Empfehlungsgrade und Symbolik der NVL

Evidenzgrad (analog zu NICE)	Vereinfachte Definition der Quellen	Empfehlungsgrad S3/NVL	Symbol NVL	Beschreibung
I	Metaanalysen; hochwertige randomisierte kontrollierte Studien	A	⇑⇑	Starke Empfehlung
II oder III	Kontrollierte Studien ohne Randomisierung; Beobachtungs-Studien	B	⇑	Empfehlung
IV	Expertenmeinung	0	⇔	Empfehlung offen
-	Klinischer Konsenspunkt*	KKP*	-	Gute klinische Praxis*

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Empfehlungen

Therapiegrundsätze für die Akutbehandlung

Empfehlung/Statement	Empfehlungs-grad
3-6_mod_2015 Bei einer leichten depressiven Episode kann, wenn anzunehmen ist, dass die Symptomatik auch ohne aktive Behandlung abklingt, im Sinne einer aktiv-abwartenden Begleitung zunächst von einer depressionsspezifischen Behandlung abgesehen werden. LoE IV: Expertenkonsens basierend auf Referenzleitlinie [409]	0

Empfehlung/Statement	Empfehlungs-grad
3-7_mod_2015 Hält die Symptomatik einer leichten depressiven Episode nach einer Kontrolle nach spätestens 14 Tagen noch an oder hat sie sich verschlechtert, soll mit dem Patienten über eine Intensivierung der Behandlung gesprochen werden. Als Behandlungsmöglichkeiten stehen beispielsweise zur Verfügung: • Beratung (Counselling); • psychoedukativ-supportive Gespräche; • qualifizierte angeleitete Selbsthilfe z. B. Selbsthilfebücher/Online-Programme; • Problemlöseansätze (Problem-solving); • psychiatrisch-psychotherapeutische Basisbehandlung bzw. psychosomatische Grundversorgung. LoE IV: Expertenkonsens basierend auf Referenzleitlinie [409]	0
3-8 Antidepressiva sollten nicht generell zur Erstbehandlung bei leichten depressiven Episoden eingesetzt werden, sondern allenfalls unter besonders kritischer Abwägung des Nutzen-Risiko-Verhältnisses. LoE Ib: Metaanalysen [431; 445]	B
3-9_mod_2015 Für einen Einsatz von Antidepressiva bei einer leichten depressiven Episode können u. a. sprechen: • Wunsch/Präferenz des Patienten; • positive Erfahrung des Patienten mit gutem Ansprechen auf eine medikamentöse Therapie in der Vergangenheit; • Fortbestehen von Symptomen nach anderen Interventionen; • Episoden mittelgradiger oder schwerer Depression in der Vorgeschichte des Patienten. Expertenkonsens	KKP

Empfehlung/Statement	Empfehlungs-grad
3-10 Zur Behandlung einer akuten mittelgradigen depressiven Episode soll Patienten eine medikamentöse Therapie mit einem Antidepressivum angeboten werden. LoE Ia: Metaanalysen [360; 462; 465; 473; 492; 574; 575]	A

Empfehlung/Statement	Empfehlungs-grad
3-11 Bei akuten schweren depressiven Episoden soll eine Kombinationsbehandlung mit medikamentöser Therapie und Psychotherapie angeboten werden. LoE Ia: Metaanalysen [576; 580] und RCTs [577-579]	A

Empfehlung/Statement	Empfehlungs-grad
3-12 Wenn bei leichten oder mittelgradigen depressiven Episoden eine Pharmakotherapie erwogen wird, kann bei Beachtung der spezifischen Nebenwirkungen und Interaktionen ein erster Therapieversuch auch mit Johanniskraut unternommen werden. LoE IV: Expertenkonsens basierend auf einer Metaanalyse [543]	**0**
3-13 Patienten, die Johanniskraut einnehmen, sollten über die unterschiedliche Wirkstärke der verfügbaren Zubereitungen und die sich daraus ergebenden Unsicherheiten informiert werden. Sie sollten ebenfalls aufgeklärt werden über mögliche schwere Wechselwirkungen von Johanniskraut mit anderen Medikamenten (einschließlich oraler Kontrazeptiva, Antikoagulantien und Antiepileptika). LoE IV: Expertenkonsens	**B**

Empfehlung/Statement	Empfehlungs-grad
3-14 NEU 2015 **Zeitlicher Ablauf einer Antidepressiva-Behandlung** Ab Erreichen der Standarddosierung sollten vier Wochen (bei älteren Patienten: sechs Wochen) wegen der Wirklatenz abgewartet werden, bis gemeinsam mit dem Patienten beurteilt wird, ob eine Response vorliegt. Hierzu ist eine gute Dokumentation der Symptomatik bei Behandlungsbeginn erforderlich. Dieser Bewertungstag sollte bereits zu Beginn der Medikation mit dem Patienten vereinbart werden. Bei vielen Antidepressiva sollte schrittweise bis zur Standarddosierung aufdosiert werden. Diese Aufdosierungsphase sollte so lange sein, wie es die Verträglichkeit erfordert, aber so kurz wie möglich, da diese Zeit nicht zur Wirklatenz hinzu gezählt werden kann. Während der Aufdosierungsphase und der Beobachtung der Wirklatenz sollte eine sorgfältige Überwachung möglicher Nebenwirkungen erfolgen. Bei Response am Entscheidungstag sollte die Fortsetzung der Medikation bis zur Remission mit anschließendem Übergang in die Erhaltungstherapie erfolgen. Bei Non-Response sollte dem Patienten eine Veränderung der Behandlungsstrategie empfohlen werden. Expertenkonsens	**KKP**

Empfehlung/Statement	Empfehlungs-grad
3-15 mod 2015 In der Regel sollte die antidepressive Medikation mit der niedrigen, als „Anfangsdosis" bezeichneten Tagesdosis begonnen werden. Bei älteren Patienten ist es sinnvoll, bei Trizyklika diese Anfangsdosis zu halbieren und gegebenenfalls langsam aufzudosieren. Expertenkonsens	KKP
3-16 mod 2015 Bei trizyklischen Antidepressiva sind deren anticholinerge und chinidinartige Nebenwirkungen zu beachten. Daher ist deren Gabe für Patienten mit kardiovaskulärer Erkrankung, Engwinkelglaukom, Prostatahypertophie, Pylorusstenose und anderen ausgeprägten intestinalen Stenosen, schwerer Obstipation, kognitiven Störungen, Krampfleiden oder Verwirrtheitszuständen/Delir mit einem erhöhten Risiko verbunden. Expertenkonsens basierend auf Metaanalyse von RCTs [360] und Beobachtungsstudien [468-470]	KKP
3-17 mod 2015 Besonders zu Beginn der Therapie mit SSRI sollte auf • Hinweise auf ein Serotoninsyndrom (Verwirrtheit, Delir, Zittern/Frösteln, Schwitzen, Veränderungen des Blutdrucks, Myoklonus und Mydriasis); • Blutungsneigung, insbesondere bei gleichzeitiger Gabe von nichtsteroidalen Antirheumatika; • Hyponatriämie v. a. bei älteren Patienten (SIADH = vermehrte Produktion oder Wirkung des antidiuretischen Hormons ADH); • Diarrhöe; • Suizidgedanken; • eine erhebliche Zunahme von motorischer Unruhe und von Angst und Agitiertheit geachtet werden. Die Patienten sollten auf die Möglichkeit solcher Symptome zu Beginn der medikamentösen Behandlung hingewiesen werden und bei deren Auftreten umgehend ärztliche Hilfe in Anspruch nehmen. LoE Ib: Metaanalyse von RCTs [477] Metaanalyse von Beobachtungsstudien [480] und RCTs [475; 476]	B

Empfehlung/Statement	Empfehlungs-grad
3-18 mod 2015 Eine intensive Aufklärung und engmaschige Betreuung (wöchentlich) sollte in den ersten vier Wochen erfolgen, um die Mitarbeit des Patienten zu fördern. Wichtige Inhalte des Aufklärungsgesprächs sind: • Bedenken gegenüber Antidepressiva (z. B. Sucht-, Toleranzentwicklung, Persönlichkeitsveränderungen) erkennen und besprechen; • biologische Wirkmechanismen erklären; • auf Wirklatenz und mögliche Wechselwirkungen mit anderen Medikamenten hinweisen; • Nebenwirkungen erläutern; • Behandlungsdauer begründen. Außerdem kann es dabei vorteilhaft sein, Angehörige und/oder Selbsthilfegruppen einzubeziehen. Expertenkonsens	KKP

Empfehlung/Statement	Empfehlungs-grad
3-19 mod 2015 In den ersten 4 Behandlungswochen wird ein wöchentliches Monitoring, danach in Intervallen von 2-4 Wochen und nach 3 Monate in längeren Intervallen, empfohlen. • Spätestens nach 4 Wochen sollte eine genaue Wirkungsprüfung erfolgen und entschieden werden, ob ein Wechsel oder eine Ergänzung der Behandlungsstrategie indiziert ist oder nicht. • Ist keine Verbesserung erkennbar, sollten die Mitarbeit des Patienten und bei den dafür in Frage kommenden Medikamenten der Plasmaspiegel geprüft werden. • Grundsätzlich angeraten sind Plasmaspiegelkontrollen bei Behandlung mit der Maximaldosis, Verträglichkeitsproblemen, multimedizierten oder komorbiden Patienten, Symptomverschlechterung bei dosisstabiler antidepressiver Medikation und Non-Respondern bzw. Problemen in der Mitarbeit des Patienten. • Im Fall des ausbleibenden erwarteten Therapieeffekts ist das Monitoring der Konzentrationen von Antidepressiva im Serum inzwischen für die meisten Antidepressiva gut etabliert (Ausnahmen: nicht etabliert für Tranylcypromin und Agomelatin, eingeschränkt etabliert für Paroxetin, Mianserin und Bupropion). • Bei Beginn einer Medikation mit Antidepressiva sollten Blutbild und Transaminasen untersucht werden. • Bei Gabe von Lithium sind initial und im Verlauf der Kreatininwert, die Kreatinin-Clearance, die Elektrolyte (inkl. Calcium) und das Erfassen der Schilddrüsengröße sowie der TSH-Wert wichtig. • Gewichtskontrollen sind bei einigen Pharmaka wegen der möglichen Gewichtszunahme wichtig, vor allem unter Mirtazapin und den meisten Trizyklika (z. B. Trimipramin und Amitriptylin) sowie Lithium. • Wegen der chinidinartigen Effekte von TZA auf die Reizleitung mit der Gefahr von Blockbildungen und Arrhythmien sowie wegen des Risikos der QTc-Zeit-Verlängerung unter SSRI (insb. in höheren Dosierungen) sind vor Behandlungsbeginn, nach Aufdosierung und in Abhängigkeit von Dosierung und Risiko auch im Verlauf EKG-Kontrollen notwendig. • Jedem Patient, der mit Antidepressiva behandelt wird, sollte zu Beginn der Behandlung besondere Aufmerksamkeit gewidmet und auf mögliche Symptome, die auf eine Erhöhung des Suizidrisikos hindeuten, geachtet werden. • Beim Absetzen der Medikation sollten Antidepressiva in der Regel schrittweise über einen Zeitraum von 4 Wochen reduziert werden. Expertenkonsens basierend auf Referenzleitlinien [221; 226; 241; 478; 595]	KKP

Erhaltungstherapie:

Empfehlung/Statement	Empfehlungs-grad
3-20 Antidepressiva sollen mindestens 4-9 Monate über die Remission einer depressiven Episode hinaus eingenommen werden, weil sich hierdurch das Risiko eines Rückfalls erheblich vermindern lässt. In dieser Erhaltungsphase soll die gleiche Dosierung wie in der Akutphase fortgeführt werden. LoE Ia: Metaanalysen [292; 562] und RCTs [93; 93; 602; 603; 608-611].	A

Empfehlung/Statement	Empfehlungs-grad
3-21 Patienten mit 2 oder mehr depressiven Episoden mit bedeutsamen funktionellen Einschränkungen in der jüngeren Vergangenheit sollten dazu angehalten werden, das Antidepressivum mindestens 2 Jahre lang zur Langzeitprophylaxe einzunehmen. LoE Ia: Metaanalysen [605; 623-625] und RCTs [297; 606; 618-622]	B
3-22 Zur Vorbeugung eines Rezidivs sollte die gleiche Dosierung des Antidepressivums verabreicht werden, die bei der Akuttherapie wirksam war. LoE Ia: RCTs [608; 622] und Referenzleitlinie [615]	0

Empfehlung/Statement	Empfehlungs-grad
3-23 Bei suizidgefährdeten Patienten soll in der Rezidivprophylaxe zur Reduzierung suizidaler Handlungen (Suizidversuche und Suizide) eine Medikation mit Lithium in Betracht gezogen werden. LoE Ia: Metaanalyse [534]	A

Maßnahmen bei Nichtansprechen

Empfehlung/Statement	Empfehlungs-grad
3-24 mod 2015 Spricht ein Patient nach 4 Wochen nicht auf eine Antidepressivamonotherapie an, sollten zunächst Ursachen für diesen Verlauf evaluiert werden. Zu diesen Ursachen gehören gegebenenfalls die nicht ausreichende Mitarbeit des Patienten, eine nicht angemessene Dosis und ein zu niedriger Serumspiegel. LoE III: Beobachtungsstudien [647; 648] und Referenzleitlinien [644-646]	B

Empfehlung/Statement	Empfehlungs-grad
3-25 NEU 2015 **Serumspiegelkontrolle von Antidepressiva (TDM)** Spricht ein Patient nach angemessener Behandlungsdauer und -dosis sowie bestimmungsgemäßer Einnahme nicht auf eine Antidepressiva-Medikation an, sollte der Plasmaspiegel des Medikaments kontrolliert werden. Für die meisten Antidepressiva sind inzwischen Empfehlungen für einen therapeutischen Plasmaspiegel etabliert. Die Blutabnahme soll im steady state (das ist bei den allermeisten Antidepressiva vier bis fünf Tage nach Einnahme einer konstanten Dosierung) und als so genannter Talspiegel erfolgen. Sowohl ein zu niedriger als auch ein zu hoher Plasmaspiegel sollte im Sinne des Therapeutischen Drug Monitorings (TDM) durch eine Dosisadaptation korrigiert werden. Ferner sind Plasmaspiegelkontrollen angeraten bei Hochdosisbehandlung, Verträglichkeitsproblemen, multimedizierten oder komorbiden Patienten, Symptomverschlechterung bei dosisstabiler antidepressiver Medikation und unsicherer Einnahmeregelmäßigkeit. Expertenkonsens basierend auf Referenzleitlinien [595; 649; 650]	KKP

Empfehlung/Statement	Empfehlungs-grad
3-26 Bei zahlreichen Antidepressiva (z. B. TZA, Venlafaxin, Tranylcypromin) kann eine sinnvolle Maßnahme bei Non-Response im Aufdosieren der Substanz im Einklang mit den Anwendungsempfehlungen des Herstellers bestehen. Dies gilt nicht für SSRI. LoE Ib: Metaanalyse [654]	0

Empfehlung/Statement	Empfehlungs-grad
3-27 Ein Versuch zur Wirkungsverstärkung (Augmentation) mit Lithium sollte vom erfahrenen Arzt bei Patienten erwogen werden, deren Depression auf Antidepressiva nicht angesprochen hat. LoE Ia: Metaanalysen [655-657]	B
3-28 Wenn bei einem Patienten 2-4 Wochen nach Erreichen wirksamer Lithiumspiegel keine Wirkung festzustellen ist, sollte Lithium wieder abgesetzt werden. Expertenkonsens	KKP

Empfehlung/Statement	Empfehlungs-grad
3-29 Patienten, die gut auf ein Antidepressivum mit Lithium-Augmentation ansprachen, sollten unter diesem Regime für mindestens 6 Monate bleiben. LoE IV: Expertenkonsens	B
3-30 mod 2015 Die Augmentation von Antidepressiva mittels Carbamazepin, Lamotrigin, Pindolol, Valproat, Dopaminagonisten, Psychostimulanzien, Schilddrüsen- oder anderen Hormonen kann nicht als Routineeinsatz bei therapieresistenter Depression empfohlen werden. LoE Ib: RCT [659] und Referenzleitlinie [658]	0
3-31 NEU 2015 Bei Patienten, die nicht auf eine Monotherapie mit Antidepressiva ansprechen, sollte eine Augmentation von Antidepressiva mit den Antipsychotika Quetiapin (zugelassen), Aripiprazol, Olanzapin und Risperidon (jeweils off-label) in verhältnismäßig niedrigen Dosierungen erwogen werden, um depressive Symptome zu reduzieren. LoE Ia: Metaanalysen [668-670]	B

Empfehlung/Statement	Empfehlungs-grad
3-32 Beim Wechsel zwischen Antidepressiva sollten wegen möglicher Wechselwirkungen eine schrittweise Aufdosierung des neuen und ein ausschleichendes Absetzen des alten Antidepressivums erfolgen. LoE IV: Expertenkonsens	B
3-33 Der Wechsel des Antidepressivums ist bei Nichtansprechen nicht die Behandlungsalternative erster Wahl. Jeder Wechsel sollte daher sorgfältig geprüft werden. LoE Ib: Metaanalyse [676], RCTs [673-675; 677; 678] und Beobachtungsstudien [577; 644; 645; 658]	B

Empfehlung/Statement	Empfehlungs-grad
3-34 mod 2015 Bei der Umstellung von SSRIs, SNRI und Clomipramin auf MAO-Hemmer ist ein ausreichender Sicherheitsabstand von 2 Wochen, bei Fluoxetin von 5 Wochen zu berücksichtigen. Eine Kombination der MAO-Hemmer mit diesen Antidepressiva ist kontraindiziert. Expertenkonsens	KKP

Empfehlung/Statement	Empfehlungs-grad
3-35 mod 2015 Bei einem Patienten, der auf eine Antidepressivamonotherapie nicht respondiert hat, kann als einzige Antidepressivakombination die Kombination von Mianserin (unter Berücksichtigung des Agranulozytoserisikos) oder Mirtazapin einerseits mit einem SSRI oder einem TZA andererseits empfohlen werden. Nur für diese Kombinationen wurde in mehreren randomisierten und doppelblinden Studien gezeigt, dass sie wirksamer sind als die Monotherapie mit nur einem der Wirkstoffe. Expertenkonsens basierend auf Metaanalysen [685; 686] und RCTs [675; 679-684]	KKP

Effektivität von Psychotherapie bei behandlungsresistenter Depression

Empfehlung/Statement	Empfehlungs-grad
3-54 Bei pharmakotherapieresistenter Depression sollte den Patienten eine angemessene Psychotherapie angeboten werden. LoE Ib: syst. Übersichtsarbeiten [957; 958]	B

Elektrokonvulsive Therapie (EKT)

Empfehlung/Statement	Empfehlungs-grad
3-55_mod_2015 EKT soll bei schweren, vital bedrohlichen oder therapieresistenten depressiven Episoden als Behandlungsalternative in Betracht gezogen werden. LoE Ia: Metaanalysen [973; 978]	A

Empfehlung/Statement	Empfehlungs-grad
3-56_NEU_2015 Nach einer erfolgreichen EKT-Behandlungsserie sollte eine Erhaltungstherapie mit Pharmakotherapie und Psychotherapie erfolgen, mit oder ohne zusätzliche EKT. LoE Ia: Metaanalysen [1016; 1018; 1019]	B
3-57_mod_2015 Eine EKT-Erhaltungstherapie nach einer erfolgreichen EKT-Behandlungsserie sollte eingesetzt werden bei Patienten, die • unter einer adäquaten sonstigen Rezidivprophylaxe in der Anamnese einen Rückfall erlitten hatten bzw. • eine Unverträglichkeit gegenüber einer Rezidivprophylaxe aufweisen bzw. • eine entsprechende Präferenz haben. LoE Ib: Metaanalysen [1018; 1019], RCT [1017] und Referenzleitlinien [864; 988]	B

Detaillierte Darstellung der Recherchestrategie

Cochrane Library **(Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 14.12.2017**

#	Suchfrage
1	[mh “Depressive Disorder”/TH,DT]
2	[mh Depression/TH,DT]
3	(depression or depressive or depressed or dysthymi*):ti
4	(affective disorder*):ti or (mood disorder*):ti or (unipolar disorder*):ti
5	#1 or #2 or #3 or #4
6	#5 Publication Year from 2012 to 2017

SR, HTAs in Medline (PubMed) am 14.12.2017

#	Suchfrage
1	(''depressive disorder/drug therapy''[majr]) OR ''depression/drug therapy''[majr]
2	(((depression[ti]) OR depressive[ti]) OR depressed[ti]) OR dysthymi*[ti]
3	affective disorder*[ti] OR mood disorder*[ti] OR unipolar disorder*[ti]
4	agents, antidepressive[mh]
5	((((((((((treatment*[ti]) OR therapy[ti]) OR therapies[ti]) OR therapeutic[ti]) OR monotherap*[ti]) OR polytherap*[ti]) OR pharmacotherap*[ti]) OR effect*[ti]) OR efficacy[ti]) OR treating[ti]) OR treated[ti]) OR management[ti]) OR treat*[ti] OR antidepress*[tiab] OR anti-depress*[tiab]
6	(serotonin[tiab]) AND inhibitor*[tiab]
7	#2 OR #3
8	#4 OR #5 OR #6
9	#1 OR (#7 AND #8)
10	(#9) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))
11	((#10) AND (''2012/12/01''[PDAT] : ''2017/12/31''[PDAT]) NOT ''The Cochrane database of systematic reviews''[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 14.12.2017

#	Suchfrage
1	(''depressive disorder/drug therapy''[majr]) OR ''depression/drug therapy''[majr]
2	(((depression[ti]) OR depressive[ti]) OR depressed[ti]) OR dysthymi*[ti]
3	affective disorder*[ti] OR mood disorder*[ti] OR unipolar disorder*[ti]
4	#1 OR #2 OR #3
5	(#4) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR

	Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[Title])*
6	(((#5) AND ("2012/12/01"[PDAT] : "2017/12/31"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]))

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Anhang

Studiencharakteristiken Quelle Karyotaki et al. 2016 [14]

Table 2
Studies characteristics.

Studies	Recruitment	Design	Any AXIS-II Diagnosis (%/ Total N)	PT	*N* patients	Comparison	*N* patients	FU (months)	Outcome	Type of treatment	RA[a]	Risk of bias[b] (0–7)	Country
Beck et al., 1985	CS	RCT	9%	CBT & TCA	15	CBT	18	6, 12	BDI, HRSD	Acute	1	5	US
Bellino et al., 2006	CS	RCT	100%	IPT & SSRI	20	SSRI	19	6	Remission (HRSD scores reduction ≥ 40%)	Acute	0	3	IT
Blackburn et al., 1986	CS	RCT/nat.FU	NR	CBT & TCA	16	TCA CBT	10 15	6, 12, 18, 24	Response (HRSD < 8; BDI < 9)	Acute	0	5	UK
De Jonghe et al., 2001	CS	RCT	NR	PDST & SSRI	83	SSRI	84	6	Remission (HRSD < 8)	Acute	1	4	NL
De Jonghe et al., 2004	CS	RCT	NR	PDST & TCA/SSRI	101	PDST	107	6	Remission (HRSD ≤ 7),	Acute	0	3	NL
Frank et al., 1990	CS	RCT	NR	IPT & TCA	25	TCA	28	12, 24, 36	Recurrence (HRSD ≥ 15); survivors (HRSD < 15; Raskin < 7)	Maintenance	0	4	US
Hersen et al., 1984	Com. S	RCT	NR	SS & TCA	21	TCA	14	6	Depressive symptoms (BDI; HRSD; REDS)	Maintenance	1	4	US
Hollon et al., 1992; Evans, 1992	CS	RCT	NR	CBT & TCA	13	TCA CBT	10 10	24	Relapse (BDI ≥ 16)	Acute	0	4	US
Hollon et al., 2014	CS	RCT	49.8%	CBT & ADM (NS)	187	ADM (NS)	170	12	Recovery (> 26 consecutive weeks without relapse)	Maintenance	0	1	US
Macaskill and Macaskill, 1996	CS	RCT	65%	RET & TCA	10	TCA	10	6	HRSD; BDI	Acute	0	4	UK
Maina et al., 2009	CS	RCT	NR	BDT & SSRI	65	SSRI	83	48	Remission (HRSD ≤ 7)	Acute	0	4	IT
Maina et al., 2010	Com. & CS	RCT	NR	BDT & SSRI	25	SSRI	29	12	Remission (HRSD ≤ 7),	Acute	0	3	IT
Miller et al., 1989	Inpatients	RCT/nat.FU	NR	CBT & TCA	28	TCA	17	6, 12	Remission (HRDS ≤ 7; BDI ≤ 9),	Acute	0	3	US
Mynors-Wallis et al., 2000	CS	RCT	NR	PST & SSRI	35	SSRI PST (GP) PST (nurse)	36 39 41	13	Recovery (HRSD-17 ≤ 7)	Acute	1	1	UK
Paykel et al., 1999	CS	RCT	NR	CBT & TCA	80	TCA	78	17	Relapse (DSM-III-R)	Maintenance	0	3	UK
Perlis et al., 2002	NR	RCT	NR	CBT &SSRI	66	SSRI	66	6	Relapse (HRSD ≥ 15)	Maintenance	0	4	US
Reynolds et al., 1999	NR	RCT	NR	IPT & TCA	16	TCA	25	12	Remission (DSM-IV)	Maintenance	0	4	US
Reynolds et al., 2006	CS	RCT	NR	IPT & SSRI	22	SSRI	24	12	Recurrence (DSM-IV)	Maintenance	1	3	US
Schramm et al., 2007	Inpatients	RCT/nat.FU	21%	IPT & TCA	65	TCA	65	12	Response (HRSD scores reduction ≥ 50%); Recovery (HRSD ≤ 7)	Acute	0	3	DE
Simons et al., 1986	CS	RCT/nat.FU	NR	CBT & TCA	18	TCA CBT	16 19	12	Response (BDI < 10)	Acute	0	4	US
Sirey et al., 2005	CS	RCT	NR	CBT & ADM (NS)	21	ADM (NS)	24	6	Response (HRSD ≤ 10	Acute	1	4	US
Wilkinson et al., 2009	CS	RCT	NR	CBT & SSRI	22	SSRI or TCA	23	6, 12	Recurrence (MADRS ≥ 10; BDI ≥ 12)	Maintenance	1	1	UK
Zu et al., 2014	CS	RCT	NR	CBT SSRI	60	SSRI CBT	60 30	6	Remission QIDS < 5	Acute	0	4	CH

ADM: Antidepressant Medication; BDI: Beck Depression Inventory; BDT: Brief Dynamic Therapy; CBT: Cognitive Behavioral Therapy; CH: China; CIDI: Composite International Clinical Interview; Com. S: Community Sample CS: Clinical Sample; GP: General Practitioner; DE: Germany; DSM: Diagnostic and Statistical Manual of Mental Disorders; FU: Follow Up postrandomization; GP: General Practitioner; HRSD: Hamilton Rating Scale for Depression; IPT: Interpersonal Psychotherapy; IT: Italy; M: month(s); MADRS: Montgomery Asberg Depression Rating Scale; N: number; NL: Netherlands; NR: Not Reported; NS: Not Specified; PDST: Psychodynamic Supportive Therapy; PST: Problem Solving Therapy; PT: Psychotherapy; QIDS:Quick Inventory of Depressive Symptomatology-Self- Report; RA: Research Allegiance; RCT: Randomized Controlled Trial; RCT/nat. FU: Randomized Controlled Trial/Naturalistic Follow Up; SSRI: Selective Serotonin Reuptake Inhibitor; TCA: Tricyclic antidepressant; UK: United Kingdom; US: United States; W: week(s).

[a] One (1) is given when the study was evaluated as at high risk of researcher allegiance and zero (0) when the study was evaluated as at low risk of researcher allegiance.

[b] Sum of 'unclear or high risk of bias' of the individual quality criteria. The sum is derived after assigning a zero (low risk of bias) or one (unclear or high risk of bias) to each one of the following quality criteria: allocation sequence, allocation concealment, blinding of participants and personnel, blinding of assessors, incomplete outcome data, selective reporting, and other sources of bias.

Lister der eingeschlossenen Studien in Brignone et al. 2016 [2]

Table 2. List of the 27 included studies in the systematic literature review.

Study	N	Intervention	Comparator	Duration (weeks)	NICE quality assessment question							Linked publications
					1	2	3	4	5	6	7	
Head to head monotherapy studies												
REVIVE study[39]	501	Vortioxetine 10–20 mg	Agomelatine 25–50 mg	12								Haggstrom, 2013[40]
Kasper and Hajak, 2010[41]	177^	Agomelatine 25–50 mg	Sertraline 50–100 mg	6								Kasper and Hajak, 2013[33]
STAR*D study[21]	789	Bupropion 150–400 mg	Sertraline 50–200 mg Venlafaxine 37.5–375 mg Cognitive therapy	14								Boren, 2007; Fava, 2008; Gaynes, 2011; Gaynes, 2009; Haley, 2013; Katz, 2012; Kennedy, 2006; Perlis, 2012; Rush, 2008; Rush, 2009; Rush *et al.*, 2006; Thase, 2007; Trivedi, 2007; Trivedi, 2013; Warden, 2009; Ziffra, 2007[13,42–56]
Lenox-Smith and Jiang, 2008[57]	406	Venlafaxine ER 75–300 mg	Citalopram 20–60 mg	12								
Rosso, 2012[58]	49	Bupropion 150–300 mg	Duloxetine 60–120 mg	6								
Birkenhager, 2004[59]	58	Phenelzine 20–100 mg	Tranylcypromine 20–100 mg	5								
Placebo-controlled studies												
AK1102356 study, 2009[28]	325	Bupropion SR 200–300 mg	Placebo	4								–
Kasper, 2007[32]	94^	Agomelatine 25–50 mg	Placebo	NR								Kasper and Hajak, 2013[33]
Dose escalation studies												
Perahia, 2009[60]	368	Duloxetine 60–120 mg direct switch	Duloxetine 60–120 mg tapered switch	>6								Perahia, 2008[61]
Thase, 2006[62]	232	Venlafaxine 309 mg	Venlafaxine 148 mg	NR								–
Single switch arm												
Bondolfi, 2008[31]	32	Venlafaxine 75–150 mg	Paroxetine 40 mg	4								–
Bose, 2012[63]	484	Duloxetine 120 mg	Escitalopram 40 mg	2								–
Nakajima, 2011[64]	41	Sertraline 50–100 mg	Paroxetine 10–40 mg	2								Nakajima, 2009[65]
Romera, 2012[66]	566	Duloxetine 60–120 mg	Escitalopram 10–20 mg	4								Menchon, 2011; Romera, 2012; Romera, 2011[67–69]
Corya, 2006[70]	119	Venlafaxine 75–375 mg	Fluoxetine 20–40 mg	7								–
Ferreri, 2001[71]	72	Mianserin 60 mg	Fluoxetine 20 mg	6								–
Souery, 2011[72]	34	Desipramine 150–200 mg	Citalopram 40 mg	4								–
No switch of treatment (dose escalation)												
Benkert, 1997[73]	86	Paroxetine 40 mg	Paroxetine 20 mg	4								–
Brecht, 2011[74]	134	Duloxetine 120 mg*	Duloxetine 60 mg	4								–
Costa e Silva, 1998[75]	97	Venlafaxine 75–150 mg	Fluoxetine 20–40 mg	3								–
Dornseif, 1989[76]	371	Fluoxetine 60 mg	Fluoxetine 20 mg	3								–
Kornstein, 2008[77]	255	Duloxetine 120 mg	Duloxetine 60 mg	6								–
Licht *et al.*, 2001[78]	197	Sertraline 100 mg	Sertraline 200 mg	4								
Ruhe, 2009[79]	60	Paroxetine 30–50 mg	Paroxetine 20 mg	6								Mocking, 2014; Ruhe, 2012[80,81]
Schweizer, 1990[82]	77	Fluoxetine 60 mg	Fluoxetine 20 mg	3								–
Schweizer, 2001[83]	75	Sertraline 150 mg	Sertraline 50 mg	3								–
Suri, 2000[84]	30	Fluoxetine 40 mg	Sertraline 100 mg Sertraline 200 mg	6								–

*NICE checklist questions: 1: Was randomization carried out appropriately? 2: Was the concealment of treatment allocation adequate? 3: Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease? 4: Were the care providers, participants, and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)? 5: Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for? 6: Is there any evidence to suggest that the authors measured more outcomes than they reported? 7: Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
NICE: National Institute of Health and Care Excellence; NR: not reported; SR: standard release; XR: extended release.
^: subgroups of previously treated patients; Black and hatched box: low risk of bias; grey box: not clear; black box: high risk of bias.