Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2018-B-195 Esketaminhydrochlorid

Stand: Oktober 2018

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

Esketamin
[Akute Kurzzeitbehandlung der Depression]

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. Zugelassene Arzneimittel im Anwendungsgebiet*
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) • Schlafentzugstherapie
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Es liegen keine Beschlüsse zum Anwendungsgebiet „akute Kurzzeitbehandlung der Depression“ vor. Beschlüsse zu Antidepressiva: • 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	Geplantes Anwendungsgebiet laut Beratungsanforderung: HANDELSNAME ist zur akuten Kurzzeitbehandlung für die rasche Verringerung der Symptome einer Major Depression, einschließlich Suizidgedanken, bei Erwachsenen mit unmittelbarer Suizidgefahr zugelassen..
Arzneimittel mit Zulassung im Anwendungsgebiet „Depression“	
Imipramin N06AA02 Imipramin-neuraxpharm®	Depressive Syndrome unabhängig von ihrer nosologischen Zuordnung.
Clomipramin, N06AA04 Anafranil®	Depressive Erkrankungen Anafranil wird angewendet bei Erwachsenen (10 mg, 25 mg, 75 mg).
Trimipramin N06AA06 Stangyl®	Depressive Erkrankungen (Episoden einer Major Depression) mit den Leitsymptomen Schlafstörungen, Angst, innere Unruhe.
Amitriptylin, N06AA09 Saroten®	Saroten Tabs 50 mg / Saroten retard Tabs 75 mg wird angewendet: - zur Behandlung von depressiven Erkrankungen (Episoden einer Major Depression) bei Erwachsenen *Injektionslösung:* Saroten 2 ml wird angewendet zur stationären Behandlung depressiver Erkrankungen (Episoden einer Major Depression) bei Erwachsenen.
Nortriptylin N06AA10 Nortrilen®	Depressive Zustandsbilder jeder Ätiologie, vor allem, wenn sie durch vitale Hemmung und Antriebsverarmung gekennzeichnet sind.

II. Zugelassene Arzneimittel im Anwendungsgebiet

Doxepin N06AA12 Aponal®	Depressive Erkrankungen *Injektionslösung:* Zur Initialtherapie schwerer Verläufe der nachfolgend genannten Erkrankungen, wenn eine sofortige Sedierung erwünscht ist bzw. wenn eine orale Behandlung mit Doxepin nicht möglich ist oder der Patient auf diese nicht anspricht: – Depressive Erkrankungen […]
Maprotilin N06AA21 Ludiomil®	Depressive Erkrankungen. Ludiomil® wird angewendet bei Erwachsenen.
Amitriptylinoxid N06AA25 Amioxid-neuraxpharm®	Behandlung depressiver Erkrankungen.
Fluoxetin N06AB03 Fluoxetin-ratiopharm®	Erwachsene – Episoden einer Major Depression
Citalopram N06AB04 Cipramil®	Behandlung depressiver Erkrankungen […]
Paroxetin N06AB05 Seroxat®	Behandlung von depressiven Erkrankungen (Episoden einer Major Depression).
Sertralin N06AB06 Zoloft®	Episoden einer Major Depression. Rezidivprophylaxe von Episoden einer Major Depression.
Fluvoxamin N06AB08 Fevarin®	Depressive Erkrankungen (Episoden einer Major Depression).

II. Zugelassene Arzneimittel im Anwendungsgebiet

Escitalopram N06AB10 Cipralex®	Behandlung von Episoden einer Major Depression.
Tranylcypromin N06AF04 Jatrosom®	Zur Behandlung von depressiven Episoden (Episoden einer Major Depression). Jatrosom® sollte als Reserveantidepressivum zum Einsatz kommen, d.h. • wenn eine adäquate Therapie mit 2 antidepressiven Standardwirkstoffen (einschließlich trizyklischer Antidepressiva) keinen ausreichenden Erfolg brachte oder • wenn solche Standardwirkstoffe kontraindiziert sind oder vom Patienten nicht vertragen werden.
Moclobemid N06AG02 Aurorix®	Medikamentös behandlungsbedürftige depressive Syndrome. Aurorix wurde in klinischen Studien überwiegend an Patienten mit einer „Major Depression“ nach DSM-III-R geprüft.
Johanniskraut N06AP01 Neuroplant®	Pflanzliches Arzneimittel zur Behandlung leichter bis mittelschwerer depressiver Episoden (Störungen).
Johanniskraut-Kombination N06AP51 Neurapas® balance	Leichte depressive Episoden mit nervöser Unruhe.
Mianserin N06AX03 Mianserin-neuraxpharm®	Depressive Störungen.

II. Zugelassene Arzneimittel im Anwendungsgebiet

Trazodon N06AX05 Trazodon-neuraxpharm®	Depressive Erkrankungen.
Mirtazapin N06AX11 Remergil® SolTab	REMERGIL SolTab ist zur Behandlung depressiver Erkrankungen (Episoden einer Major Depression) bei Erwachsenen indiziert.
Bupropion N06AX12 Elontril®	Elontril ist angezeigt zur Behandlung von Episoden einer depressiven Erkrankung (Episoden einer Major Depression).
Tianeptin N06AX14 Tianeurax®	Tianeurax® ist zur Behandlung von Depressionen indiziert. Tianeurax® ist bei Erwachsenen indiziert.
Venlafaxin N06AX16 Trevilor®	– Behandlung von Episoden einer Major-Depression – Rezidivprophylaxe von Episoden einer Major-Depression
Milnacipran N06AX17 Milnaneurax®	Behandlung von Episoden einer Major Depression bei Erwachsenen.
Reboxetin N06AX18 Edronax®	Reboxetin ist für die Behandlung akuter depressiver Erkrankungen/Major-Depression bestimmt. Die Behandlung sollte bei Patienten, die initial auf Edronax 4mg Tabletten angesprochen haben, zur Aufrechterhaltung der klinischen Besserung fortgeführt werden.
Duloxetin N06AX21 Cymbalta®	Zur Behandlung von depressiven Erkrankungen (Major Depression). Cymbalta wird angewendet bei Erwachsenen.

II. Zugelassene Arzneimittel im Anwendungsgebiet

Agomelatin N06AX22 Valdoxan®	Behandlung von Episoden einer Major Depression. Valdoxan wird angewendet bei Erwachsenen.
Vortioxetin N06AX26 Brintellix®	Brintellix® wird angewendet zur Behandlung von Episoden einer Major Depression bei Erwachsenen.
Lithiumcarbonat N05AN01 Hypnorex® retard	Bei bestimmten akuten Depressionen, z. B. bei Therapieresistenz oder Unverträglichkeit von Antidepressiva.

Quellen: ATC-Klassifikation, Fachinformationen (Stand: 06/2018)

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2018-B-195 (Esketaminhydrochlorid)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	8. Oktober 2018

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CANMAT	Canadian Network for Mood and Anxiety Treatments
ECT/EKT	Electroconvulsive therapy/ Elektrokonvulsionstherapie
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TMS	Transcranial magnetic stimulation
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Akute Kurzzeitbehandlung für die rasche Verringerung der Symptome einer Major Depression, einschließlich Suizidgedanken, bei Erwachsenen mit unmittelbarer Suizidgefahr.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Major Depression* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 17.09.2018 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, 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 1852 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 8 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

Es wurden keine Quellen identifiziert.

3.2 Cochrane Reviews

Es wurden keine Quellen identifiziert.

3.3 Systematische Reviews

Es wurden keine Quellen identifiziert.

3.4 Leitlinien

National Institute for Health & Clinical Excellence, 2009 [7].

NICE

Last updated: April 2018

Depression: the treatment and management of depression in adults (updated edition)

Leitlinienorganisation/Fragestellung

The guideline makes recommendations for the treatment and management of depression.

It aims to:

[…]

● 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

- Multidisziplinäre Leitliniengruppe mit Vertreter*innen der Psychiatrie, klinischen Psychologie, Krankenpflege und Allgemeinmedizin; akademische Expert*innen für Psychiatrie und Psychologie; und Menschen mit Depressionen und einer Pflegekraft.
- Formulierung klinischer Fragestellungen nach PICO für Interventionen
- Update der originalen Leitlinie aus 2007 mit vollständigem Evidenzupdate 2012
- Erstellung von GRADE-Evidenzprofilen
- Informale Konsensusmethoden zur Formulierung von Empfehlungen, sofern Evidenz nicht ausreichend
- **Update 2018 umfasst lediglich neuen Hinweis auf Natriumvalproat bei Schwangeren, kein Evidenzupdate**

Recherche/Suchzeitraum:

- 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)

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. Empfehlungen und Evidenz in separaten Kapiteln dargestellt. Empfehlungen ohne GoR.
- Recherchen teilweise veraltet (s. ECT).

Empfehlungen

Crisis resolution and home treatment teams

Hinweis: Literaturrecherche bis Februar 2009

Empfehlung 5.2.13.15

If a person with depression is assessed to be at risk of suicide:

● take into account toxicity in overdose if an antidepressant is prescribed or the person is taking other medication; if necessary, limit the amount of drug(s) available

● consider increasing the level of support, such as more frequent direct or telephone contacts

● consider referral to specialist mental health services [19].

19 The evidence for this recommendation has not been updated since the previous guideline. Any wording changes have been made for clarification only.

Empfehlung 5.7.5.1

Use crisis resolution and home treatment teams to manage crises for people with severe depression who present significant risk, and to deliver high-quality acute care. The teams should monitor risk as a high-priority routine activity in a way that allows people to continue their lives without disruption [31].

31 The evidence for this recommendation has not been updated since the previous guideline. Any wording changes have been made for clarification only.

Depression, antidepressants and suicide

Empfehlung 11.10.4.1

A person with depression started on antidepressants who is considered to present an increased suicide risk or is younger than 30 years (because of the potential increased prevalence of suicidal thoughts in the early stages of antidepressant treatment for this group) should normally be seen after 1 week and frequently thereafter as appropriate until the risk is no longer considered clinically important [181].

181 Ibid.

Empfehlung 11.10.4.4

Take into account toxicity in overdose when choosing an antidepressant for people at significant risk of suicide. Be aware that:

● compared with other equally effective antidepressants recommended for routine use in primary care, venlafaxine is associated with a greater risk of death from overdose

● tricyclic antidepressants (TCAs), except for lofepramine, are associated with the greatest risk in overdose.

MHRA (2006a). Venlafaxine (Efexor) – summary of basis for regulatory position. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023840&RevisionSelectionMethod=LatestReleased

MHRA (2006b). Updated prescribing advice for venlafaxine (Efexor/Efexor XL). Available at http://www.mhra.gov.uk/ (accessed May 2009).

Morgan, O., Griffiths, C., Baker, A., et al. (2004) Fatal toxicity of antidepressants in England and Wales, 1993–2003. Health Statistics Quarterly, 23, 18–24

Recognition, assessment and initial management

Empfehlung 14.3.2.4

If a person with depression is assessed to be at risk of suicide:

● take into account toxicity in overdose if an antidepressant is prescribed or the person is taking other medication; if necessary, limit the amount of drug(s) available

● consider increasing the level of support, such as more frequent direct or telephone contacts

● consider referral to specialist mental health services.

Complex and severe depression

Empfehlung 14.10.2.1

Consider inpatient treatment for people with depression who are at significant risk of suicide, self-harm or self-neglect.

Empfehlung 14.10.2.2

The full range of high-intensity psychological interventions should normally be offered in inpatient settings. However, consider increasing the intensity and duration of the interventions and ensure that they can be provided effectively and efficiently on discharge.

Empfehlung 14.10.2.3

Consider crisis resolution and home treatment teams for people with depression who might benefit from early discharge from hospital after a period of inpatient care.

Electroconvulsive therapy (ECT) [228]

Hinweis: Literaturrecherche bis Januar 2008

Empfehlung 14.10.4.1

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.

Empfehlung 14.10.4.2

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.

Empfehlung 14.10.4.3

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

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

Empfehlung 14.10.4.4

When considering ECT as a treatment choice, ensure that the person with depression is fully informed of the risks associated with ECT, and with the risks and benefits specific to them. Document the assessment and consider:

● the risks associated with a general anaesthetic current medical comorbidities

● potential adverse events, notably cognitive impairment

● the risks associated with not receiving ECT.

The risks associated with ECT may be greater in older people; exercise particular caution when considering ECT treatment in this group.

Empfehlung 14.10.4.5

A decision to use ECT should be made jointly with the person with depression as far as possible, taking into account, where applicable, the requirements of the Mental Health Act 2007. Also be aware that:

● valid informed consent should be obtained (if the person has the capacity to grant or refuse consent) without the pressure or coercion that might occur as a result of the circumstances and clinical setting

● the person should be reminded of their right to withdraw consent at any time

● there should be strict adherence to recognised guidelines about consent, and advocates or carers should be involved to facilitate informed discussions

● if informed consent is not possible, ECT should only be given if it does not conflict with a valid advance decision, and the person's advocate or carer should be consulted.

Empfehlung 14.10.4.6

The choice of electrode placement and stimulus dose related to seizure threshold should balance efficacy against the risk of cognitive impairment. Take into account that:

● bilateral ECT is more effective than unilateral ECT but may cause more cognitive impairment

● with unilateral ECT, a higher stimulus dose is associated with greater efficacy, but also increased cognitive impairment compared with a lower stimulus dose.

228 The recommendations in this section update the depression aspects only of 'Guidance on the use of electroconvulsive therapy' (NICE technology appraisal guidance 59).

Transcranial magnetic stimulation

Empfehlung 14.10.5.1

Current evidence suggests that there are no major safety concerns associated with transcranial magnetic stimulation (TMS) for severe depression. There is uncertainty about the procedure's clinical efficacy, which may depend on higher intensity, greater frequency, bilateral application and/or longer treatment durations than have appeared in the evidence to date. TMS should therefore be performed only in research studies designed to investigate these factors. [229]

229 This recommendation is taken from 'Transcranial magnetic stimulation for severe depression' (NICE interventional procedure guidance 242).

The Canadian Network for Mood and Anxiety Treatments, 2016 [3,6].

CANMAT

Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder:

- Introduction and Methods

- Section 4. Neurostimulation Treatments

Leitlinienorganisation/Fragestellung

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.
- 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

Recherche/Suchzeitraum:

- 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 systematic reviews with medical librarian consultation as needed.

LoE

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.

GoR

- GoR.nicht verwendet.

Recommendations

Table 2. Summary of Neurostimulation Treatment Recommendations for Major Depressive Disorder.

Neurostimulation	Overall Recommendation	Acute Efficacy	Maintenance Efficacy	Safety and Tolerability
rTMS	First line (for patients who have failed at least 1 antidepressant)	Level 1	Level 3	Level 1
ECT	Second line First line in some clinical situations (see Table 5)	Level 1	Level 1	Level 1
tDCS	Third line	Level 2	Level 3	Level 2
VNS	Third line	Level 3	Level 2	Level 2
DBS	Investigational	Level 3	Level 3	Level 3
MST	Investigational	Level 3	Not known	Level 3

DBS, deep brain stimulation; ECT, electroconvulsive therapy; MST, magnetic seizure therapy; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; VNS, vagus nerve stimulation.

Table 5. Clinical Indications for Electroconvulsive Therapy as a First-Line Treatment for Major Depressive Disorder.

- Acute suicidal ideation (Level 1)
- Psychotic features (Level 1)
- Treatment-resistant depression (Level 1)
- Repeated medication intolerance (Level 3)
- Catatonic features (Level 3)
- Prior favourable response to ECT (Level 3)
- Rapidly deteriorating physical status (Level 3)
- During pregnancy, for any of the above indications (Level 3)
- Patient preference (Level 4)

Hinweis: Es wurde keine Literaturstelle zugeordnet.

Bundesärztekammer, 2015 [1,2].

BäK

S3-Leitlinie/Nationale Versorgungs-Leitlinie Unipolare Depression (2. Auflage):

- Langfassung
- Leitlinienreport

Leitlinienorganisation/Fragestellung

- 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.
- Multidisziplinäre und repräsentative Leitliniengruppe

- Formale Konsensustechniken mittels nominalen Gruppenprozess: Konsens bei Zustimmung von min. 75 %, starker Konsens bei min. 95 %

Recherche/Suchzeitraum:

- Cochrane Libary und Trip Database 2009 - 10.2013 nach Systematischen Reviews

LoE

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.

GoR

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*

Empfehlungen

3.6.1 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

973. The UK ECT review group. Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. Lancet 2003;361(9360):799-808.
978. Pagnin D, de Queiroz V, Pini S, et al. Efficacy of ECT in depression: a meta-analytic review. J ECT 2004;20(1):13-20.

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

864. American Psychiatric Association (APA). The practice of electroconvulsive therapy: recommendations for treatment, training and privileging: a task force report of the American Psychiatric Association. Washington: American Psychiatric Association (APA); 2001.
988. Grözinger M, Conca A, DiPauli J, et al. Elektrokonvulsionstherapie: Psychiatrische Fachgesellschaften aus vier Ländern empfehlen einen rechtzeitigen und adäquaten Einsatz. Nervenarzt 2012;83:919-21.
1016. Jelovac A, Kolshus E, McLoughlin DM. Relapse following successful electroconvulsive therapy for major depression: a meta-analysis. Neuropsychopharmacology 2013;38(12):2467-74.
1017. Kellner CH, Knapp RG, Petrides G, et al. Continuation electroconvulsive therapy vs pharmacotherapy for relapse prevention in major depression: a multisite study from the Consortium for Research in Electroconvulsive Therapy (CORE). Arch Gen Psychiatry 2006;63(12):1337-44.
1018. Brown ED, Lee H, Scott D, et al. Efficacy of continuation/maintenance electroconvulsive therapy for the prevention of recurrence of a major depressive episode in adults with unipolar depression: a systematic review. J ECT 2014;30(3):195-202.
1019. Petrides G, Tobias KG, Kellner CH, et al. Continuation and maintenance electroconvulsive therapy for mood disorders: review of the literature. Neuropsychobiology 2011;64(3):129-40.

3.6.2 Wachtherapie (Schlafentzugstherapie)

Empfehlung/Statement	Empfehlungs-grad
3-58 Wachtherapie sollte in der Behandlung depressiver Episoden als Behandlungsform erwogen werden, wenn eine rasche, wenn auch kurz anhaltende Response therapeutisch gewünscht wird oder eine andere leitliniengerechte Behandlung ergänzt werden soll. LoE Ib: syst. Übersichtsarbeiten [1024; 1025]	**B**

1024. Leibenluft E, Wehr TA. Is sleep deprivation useful in the treatment of depression? Am J Psychiatry 1992;149(2):159-68.
1025. Kuhs H, Tolle R. Sleep deprivation therapy. Biol Psychiatry 1991;29(11):1129-48.

3.10.2 Suizidprävention und Notfallinterventionen bei Suizidalität: Hauptaspekte der Suizidprävention

- Gesprächs- und Beziehungsangebot;
- Diagnostik von Suizidalität einschließlich Risikofaktoren […];
- Klärung und Regelung der aktuellen Situation;
- Therapieplanung unter Berücksichtigung der Suizidgefahr.

Empfehlung/Statement	Empfehlungs-grad
3-113 Suizidale Patienten müssen eine besondere Beachtung und Betreuung im Sinne einer Intensivierung des zeitlichen Engagements und der therapeutischen Bindung erhalten. Das konkrete Betreuungsangebot richtet sich nach den individuellen Risikofaktoren, der Absprachefähigkeit des Patienten und Umgebungsfaktoren. Expertenkonsens	**KKP**

3.10.2.3 Krisenmanagement

Die Klärung und Regelung der aktuellen Krisensituation umfasst:

- Herstellung einer tragfähigen Beziehung, Klärung des aktuellen Anlasses und der Notwendigkeit akuter psychopharmakotherapeutischer Maßnahmen (siehe Kapitel 3.10.5 “Krisenintervention und spezifische Psychotherapien“);
- Zulassen von Trauer, Wut und Angst;
- Erkennen von Suizidalität, z. B. bei einem aktuell bestehenden Konflikt (z. B. schwere Partnerschaftsproblematik) bzw. in psychopathologischem Kontext (tiefe depressive Herabgestimmtheit, Wahnsymptomatik, schwere Hoffnungslosigkeit);
- Klärung der „sichernden Fürsorge“: Vermeiden von Alleinsein, Einbeziehung positiv erlebter Bezugspersonen und Beziehungspflege als konstante Begleiter durch die aktuelle Krise im Sinne von „Kommunikationen und Kontrolle“, ggf. Zusammenarbeit mit den entsprechenden Krisendiensten für suizidale Menschen;
- Klärung des adäquaten Behandlungssettings (ambulante, ggf. unter Einbezug ambulanter psychiatrischer Pflege [APP], teilstationäre oder stationäre Behandlung; Einweisung

freiwillig/nach Unterbringungsgesetz in stationäre Behandlung; Veranlassung indizierter medizinischer Versorgung);

- nach internistischer/chirurgischer Erstversorgung bei Suizidversuch konsiliarische Abklärung durch einen entsprechend qualifizierten Facharzt für Psychiatrie und Psychotherapie;
- weitere Hilfsmöglichkeiten aktiv klären und planen;
- psychotherapeutisch orientierte Krisenintervention: Beginn sofort (Gespräch/Beziehung), Erkennen des Anlas-ses/Auslösers;
- Verbündung mit dem Patienten gegen Existenzangst, Verlustangst, Hilflosigkeitsgefühle, usw.

3.10.3 Indikationen für eine stationäre Therapie

Empfehlung/Statement	Empfehlungs-grad
3-115 mod 2015 Eine stationäre Einweisung sollte für suizidale Patienten unbedingt erwogen werden, • die akut suizidgefährdet sind; • die nach einem Suizidversuch medizinischer Versorgung bedürfen; • die wegen der zugrundeliegenden depressiven Störung einer intensiven psychiatrischen bzw. psychotherapeutischen Behandlung bedürfen; • wenn eine hinreichend zuverlässige Einschätzung des Weiterbestehens der Suizidalität anders nicht möglich ist, oder • wenn die Etablierung einer tragfähigen therapeutischen Beziehung nicht gelingt und die Person trotz initialer Behandlung akut suizidal bleibt. LoE Ib: RCTs [1492-1499]	B

1492. Blumenthal SJ, Kupfer DJ. Suicide over the life cycle: risk factors. Assessment and treatment of suicidal patients. Washington: American Psychiatric Publishing; 1990.
1493. Salkovskis PM, Atha C, Storer D. Cognitive-behavioural problem solving in the treatment of patients who repeatedly attempt suicide. A controlled trial. Br J Psychiatry 1990;157:871-6.
1494. Dicker R, Morrissey RF, Abikoff H, et al. Hospitalizing the suicidal adolescent: decision-making criteria of psychiatric residents. J Am Acad Child Adolesc Psychiatry 1997;36(6):769-76.
1495. Hawton K, Arensman E, Townsend E, et al. Deliberate self harm: systematic review of efficacy of psychosocial and pharmacological treatments in preventing repetition. Bmj 1998;317(7156):441-7.
1496. New South Wales Health Department (NSW). Policy guidelines for the management of patients with possible suicidal behaviour for NSW health staff and staff in private hospital facilities. Sydney: NSW Department of Health; 1998.
1497. Jacobson G. The inpatient management of suicidality. San Francisco: Josey-Bass; 1999.
1498. New Zealand Guidelines Group (NZGG), Ministry of Health. The assessment and management of people at risk of suicide. Best practice evidence-based guideline summary. Wellington: New Zealand Guidelines Group (NZGG); 2003. http://www.health.govt.nz/system/files/documents/publications/suicide_guideline.pdf.
1499. van der Sande R, van Rooijen L, Buskens E, et al. Intensive in-patient and community intervention versus routine care after attempted suicide. A randomised controlled intervention study. Br J Psychiatry 1997;171:35-41.

3.10.4 Pharmakotherapie

Empfehlung/Statement	Empfehlungs-grad
3-116 Zur speziellen akuten Behandlung der Suizidalität sollten Antidepressiva nicht eingesetzt werden. LoE Ib: Metaanalysen [453; 626-630]	**B**
3-117 Antidepressiva können jedoch bei suizidalen depressiven Patienten zur Depressionsbehandlung im Rahmen der allgemeinen Empfehlungen eingesetzt werden. LoE Ib: Metaanalysen [627-629; 1506], Beobachtungsstudien [1502; 1503; 1507; 1508]	**0**
3-118 Bei einem suizidalen Patienten soll die Auswahl von Antidepressiva hinsichtlich ihres Nutzen-Risiko-Verhältnisses (Pharmaka mit Letalität in hoher Dosis, Agitationssteigerung in der Frühphase) abgewogen werden. Expertenkonsens	**KKP**

453. Khan A, Khan SR, Leventhal RM, et al. Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials: a replication analysis of the Food and Drug Administration Database. Int J Neuropsychopharmacol 2001;4(2):113-8.
626. Khan A, Warner HA, Brown WA. Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials: an analysis of the Food and Drug Administration database. Arch Gen Psychiatry 2000;57(4):311-7.
627. Khan A, Khan S, Kolts R, et al. Suicide rates in clinical trials of SSRIs, other antidepressants, and placebo: analysis of FDA reports. Am J Psychiatry 2003;160(4):790-2.
628. Fergusson D, Doucette S, Glass KC, et al. Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials. Bmj 2005;330(7488):396.
629. Gunnell D, Saperia J, Ashby D. Selective serotonin reuptake inhibitors (SSRIs) and suicide in adults: meta-analysis of drug company data from placebo controlled, randomised controlled trials submitted to the MHRA's safety review. Bmj 2005;330(7488):385.
630. Hammad TA, Laughren TP, Racoosin JA. Suicide rates in short-term randomized controlled trials of newer antidepressants. J Clin Psychopharmacol 2006;26(2):203-7.
1502. Gibbons RD, Brown CH, Hur K, et al. Relationship between antidepressants and suicide attempts: an analysis of the Veterans Health Administration data sets. Am J Psychiatry 2007;164(7):1044-9.
1503. Barbui C, Esposito E, Cipriani A. Selective serotonin reuptake inhibitors and risk of suicide: a systematic review of observational studies. CMAJ 2009;180(3):291-7.
1506. Barbui C, Furukawa TA, Cipriani A. Effectiveness of paroxetine in the treatment of acute major depression in adults: a systematic re-examination of published and unpublished data from randomized trials. CMAJ 2008;178(3):296-305.
1507. Donovan S, Kelleher MJ, Lambourn J, et al. The occurence of suicide following the prescription of antidepressant drugs. Arch Suicide Res 1999;5(3):181-92.
1508. Gunnell D, Ashby D. Antidepressants and suicide: what is the balance of benefit and harm. Bmj 2004;329(7456):34-8.

3.10.4.2 Stimmungsstabilisierer

Empfehlung/Statement	Empfehlungs-grad
3-119 In der Rezidivprophylaxe bei suizidgefährdeten Patienten soll zur Reduzierung suizidaler Handlungen (Suizidversuche und Suizide) eine Medikation mit Lithium in Betracht gezogen werden. LoE Ia: Metaanalysen [520; 533; 534]	**A**

520. Baldessarini RJ, Tondo L, Hennen J. Lithium treatment and suicide risk in major affective disorders: update and new findings. J Clin Psychiatry 2003;64(Suppl 5):44-52.

533. Cipriani A, Pretty H, Hawton K, et al. Lithium in the prevention of suicidal behavior and all-cause mortality in patients with mood disorders: a systematic review of randomized trials. Am J Psychiatry 2005;162(10):1805-19.
534. Guzzetta F, Tondo L, Centorrino F, et al. Lithium treatment reduces suicide risk in recurrent major depressive disorder. J Clin Psychiatry 2007;68(3):380-3.

3.10.4.3 Andere Substanzen

Empfehlung/Statement	Empfehlungs-grad
3-120 Eine Akutbehandlung (möglichst < 14 Tage) mit einem Benzodiazepin kann bei suizidgefährdeten Patienten in Betracht gezogen werden. LoE Ib: Metaanalyse [1517]	0
3-121 Bei suizidgefährdeten Patienten mit einer depressiven Episode mit psychotischen Merkmalen sollte die antidepressive Medikation mit einem Antipsychotikum ergänzt werden. LoE IV: Expertenkonsens basierend auf [1516]	B

1516. Pfennig A, Berghöfer A, Bauer M. Medikamentöse Behandlung der Suizidalität. Verhaltenstherapie 2005;15:29-37.
1517. Furukawa TA, Streiner DL, Young LT. Is antidepressant-benzodiazepine combination therapy clinically more useful? A meta-analytic study. J Affect Disord 2001;65(2):173-7.

3.10.5 Krisenintervention und spezifische Psychotherapien

Insgesamt ist die Studienlage zu suizidpräventiven psychotherapeutischen Strategien unzureichend. […] Studien, die explizit versucht haben, die suizidpräventive Wirksamkeit spezifischer psychotherapeutischer Ansätze zu evaluieren, sind selten [1521]. Mann et al. [1522] kommen in ihrem systematischen Review zu suizidpräventiven Strategien zum Schluss, dass positive Ergebnisse bezüglich der Reduzierung sich wiederholenden suizidalen Verhaltens für die Kognitive Verhaltenstherapie [1523], Problemlösetherapie [1493; 1524-1527], psychodynamische Kurzzeittherapie [1528] sowie intensive Nachbetreuung mit regelmäßigem Kontakt [1529] vorliegen, verglichen mit der jeweils üblichen Behandlung. Gemeinsam ist diesen suizidpräventiv wirksamen Ansätzen, dass sie spezifische, auf die Suizidalität gerichtete problemlösende und einsichtsorientierte Strategien beinhalten (vgl. [1522; 1529]). In einer systematischen Übersichtsarbeit und Metaanalyse [1530] zeigten sich Hinweise, dass psychotherapeutische Interventionen zu einer signifikanten Reduktion von Suizidversuchen im Vergleich zur Routinebehandlung führen.

Empfehlung/Statement	Empfehlungs-grad
3-122 mod 2015 Als kurzfristiges Ziel von Kriseninterventionen oder Psychotherapie bei akuter Suizidalität soll eine intensive Kontaktgestaltung und eine aktive unmittelbare Unterstützung und Entlastung des Patienten bis zum Abklingen der Krise angestrebt werden. Eine tragfähige therapeutische Beziehung kann bei suizidgefährdeten Patienten per se suizidpräventiv wirken. Expertenkonsens basierend auf [1481; 1518; 1519]	**KKP**
3-123 mod 2015 Bei suizidgefährdeten Patienten mit einer depressiven Episode sollte eine Psychotherapie angeboten werden, die zunächst auf die Suizidalität fokussiert. LoE Ia: Metaanalysen [1522; 1529; 1530]	**B**

1481. Althaus D, Hegerl U. Ursachen, Diagnose und Therapie von Suizidalität. Nervenarzt 2004;75(11):1123-34.
1493. Salkovskis PM, Atha C, Storer D. Cognitive-behavioural problem solving in the treatment of patients who repeatedly attempt suicide. A controlled trial. Br J Psychiatry 1990;157:871-6.
1521. Crawford MJ, Thomas O, Khan N, et al. Psychosocial interventions following self-harm: systematic review of their efficacy in preventing suicide. Br J Psychiatry 2007;190(1):11-7.
1522. Mann JJ, Apter A, Bertolote J, et al. Suicide prevention strategies: a systematic review. Jama 2005;294(16):2064-74.
1523. Brown GK, Ten Have T, Henriques GR, et al. Cognitive therapy for the prevention of suicide attempts: a randomized controlled trial. Jama 2005;294(5):563-70.
1524. Hawton K, McKeown S, Day A, et al. Evaluation of out-patient counselling compared with general practitioner care following overdoses. Psychol Med 1987;17(3):751-61.
1525. Gibbons JS, Butler J, Urwin P, et al. Evaluation of a social work service for self-poisoning patients. Br J Psychiatry 1978;133(2):111-8.
1526. McLeavey BC, Daly RJ, Ludgate JW, et al. Interpersonal problem-solving skills training in the treatment of self-poisoning patients. Suicide Life Threat Behav 1994;24(4):382-94.
1527. Evans MO, Morgan HG, Hayward A, et al. Crisis telephone consultation for deliberate self-harm patients: effects on repetition. Br J Psychiatry 1999;175(1):23-7.
1528. Guthrie E, Kapur N, Mackway-Jones K, et al. Randomised controlled trial of brief psychological intervention after deliberate self poisoning. Bmj 2001;323(7305):135-8.
1529. Hawton K, Townsend E, Arensman E, et al. Psychosocial versus pharmacological treatments for deliberate self harm. Cochrane Database Syst Rev 2000;CD001764.
1530. O'Connor E, Gaynes B, Burda BU, et al. Screening for Suicide Risk in Primary Care: A Systematic Evidence Review for the U.S. Preventive Services Task Force. Rockville (MD): 2013 [cited: 2016-09-14]. http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0056019.

Malhi GS et al., 2015 [4].

Royal Australian and New Zealand College of psychiatrists

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

Leitlinienorganisation/Fragestellung

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

- 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.

Recherche/Suchzeitraum:

- 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.

LoE

- Adapted from the Australian National Health and Medical Research Council (NHMRC) levels of evidence for intervention studies.

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).

GoR

- Evidence-based recommendations (EBRs): sufficient consistent evidence from intervention studies is available to support a recommendation on a given topic.
- Consensus based recommendation (CBR) formulated when:
  - (i) the existing intervention evidence base was absent, ambiguous, or of doubtful clinical impact in the Australian and New Zealand context; and
  - (ii) the guideline panel (based on collective clinical and research knowledge and experience) reached consensus on the clinical utility of the recommendations.

Empfehlungen

Hospitalisation and indications for treatment away from home

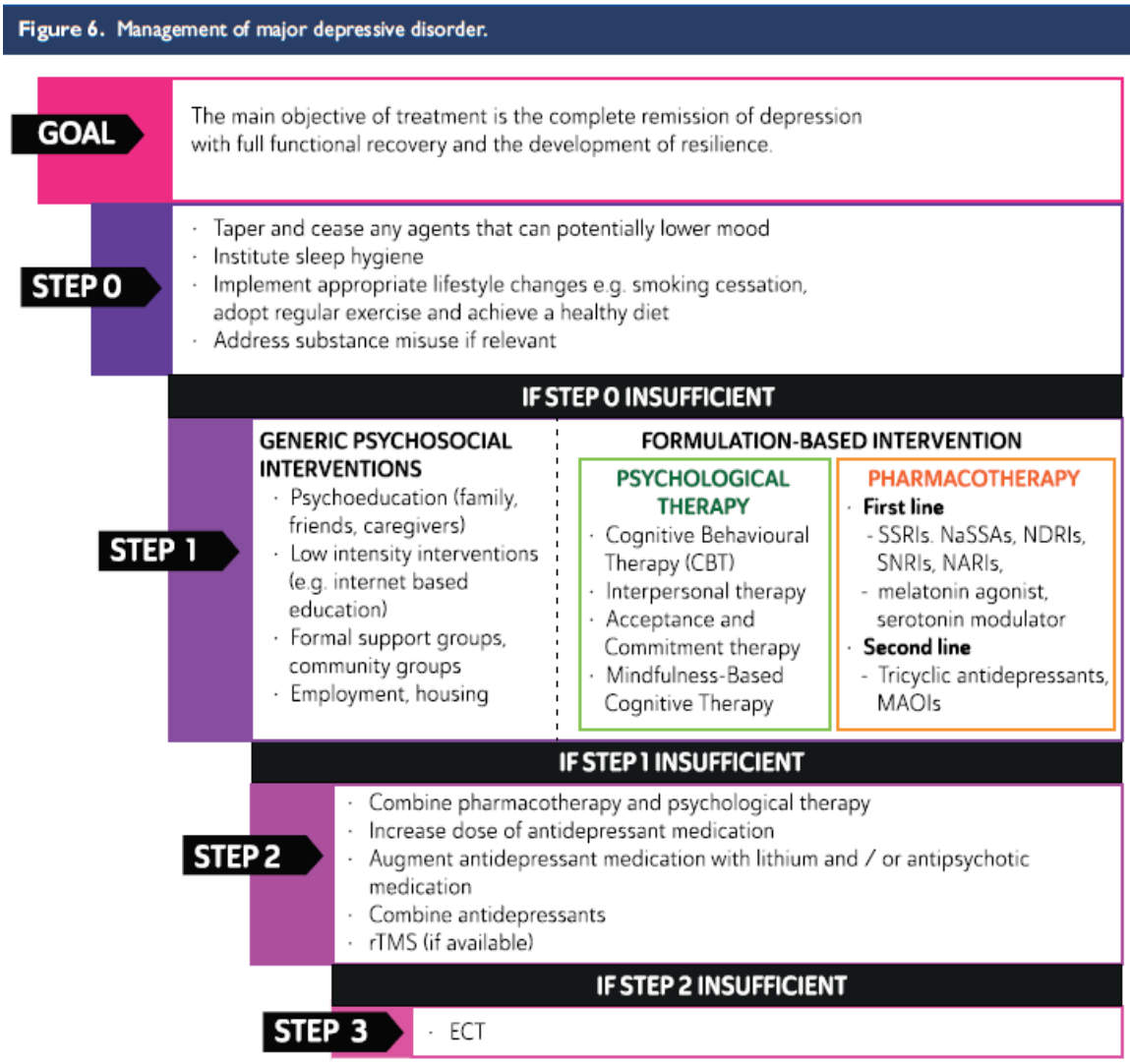
Table 10. Recommended indications for psychiatric admission.

Category of Indication	Specific Indication
Clinical Presentation	Severe depression with significant disability
	1a. Suicidal ideation with seemingly imminent risk
	1b. Medical risk (i.e., inadequate fluid intake)^
	Mania
	2a. Likelihood of escalating manic symptoms/early warning signs of imminent manic episode
	2b. Significant impulsivity or reckless disinhibition in context of mania
	Insight is severely limited to the extent that outpatient treatment is not possible
	Significant psychotic symptoms

Treatment options for severe major depressive disorder

In severe epsiodes of MDD pharmacotherapy is typically needed and, where there is a high risk of suicide or when the patient's welfare is threatened by a lack of nutrition or fluid intake, urgent intervention is sometimes necessary and may include electroconvulsive therapy (ECT). (See: Figure 6).

Figure 6. Management of major depressive disorder.



Brain stimulation methods

Electroconvulsive therapy (Level I). Electroconvulsive therapy (ECT) is a safe and effective treatment for the more severe forms of depression (Carney, 2003), where its antidepressant effect is found to be superior to medication strategies (Lisanby, 2007). Therefore, in practice it is usually reserved for patients who have not responded to several trials of medication.

ECT is recommended as first-line treatment in extremely severe melancholic depression, particularly when the patient refuses to eat or drink and/or is a **very high suicide risk**, or when the patient has very high levels of distress, has psychotic depression, catatonia or has previously responded to ECT (see: Table 16)

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.

Carney S, Cowen P, Dearness K, et al. (2003) Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. Lancet 361: 799–808.
Lisanby SH (2007) Electroconvulsive therapy for depression. New England Journal of Medicine 357: 1939–1945.

Working Group of the Clinical Practice Guideline on the Management of Depression in Adults, 2014 [8].

THE SPANISH NHS

Clinical Practice Guideline on the Management of Depression in Adults

Leitlinienorganisation/Fragestellung

- 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/Suchzeitraum:

- 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

LoE

- Assessment of the quality of quantitative studies with SIGN and CASP

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.

GoR

- Formulation of recommendations based on SIGN “formal evaluation” or “reasoned judgment” criteria.

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	
√[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

Electroconvulsive therapy

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.

51. Grupo de Trabajo de la Guía de Práctica Clínica de Prevención y Tratamiento de la Conducta Suicida. Guía de Práctica Clínica de Prevención y Tratamiento de la Conducta Suicida. Santiago de Compostela: Agencia de Evaluación de Tecnologías Sanitarias de Galicia (avalia-t); 2012. Guías de Práctica Clínica en el SNS: avalia-t Nº 2010/02.
277. National Institute for Clinical Excellence (NICE). Depression: management of depression in primary and secondary care. London: National Clinical Practice Guideline number 23; 2004.
288. Kennedy SH, Lam RW, Cohen NL, Ravindran AV. Canadian Network for Mood and Anxiety Treatments (CANMAT). Clinical guidelines for the treatment of depressive disorders. IV. Medications and other biological treatments. Can J Psychiatry. 2001;46 Suppl 1:38S-58S.

Q+	In general, there is evidence of a favourable attitude towards ECT, although a minority of patients are extremely critical of it and have negative attitudes towards it[60].
Q+	Among the main benefits of ECT are a reduction in depressive symptoms and suicidal ideation[80]. Among the main negative aspects considered by patients are the lack of information, functional losses associated with this therapy, the fear of the possible brain damage it may cause and side effects, such as memory loss[60,80].

60. Chakrabarti S, Grover S, Rajagopal R. Electroconvulsive therapy: a review of knowledge,experience and attitudes of patients concerning the treatment. World J Biol Psychiatry. 2010;11(3):525-37.
80. Smith M, Vogler J, Zarrouf F, Sheaves C, Jesse J. Electroconvulsive therapy: the struggles in the decision-making process and the aftermath of treatment. Issues Ment Health Nurs. 2009;30(9):554-9.

Efficacy and safety of SSRIs and other new generation antidepressants

Evidence summary

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].

A RCT of 74 patients with major depression at high risk of suicide evaluated the efficacy of the antidepressants in reducing suicidal ideation and behaviour. The secondary endpoint employed was the HRSD-17 (total score without the suicidal ideation item). No differences in suicidal behaviour or severity of depression were found, although the patients with greater levels of suicidal ideation at baseline and treated with paroxetine obtained a significant improvement in this variable compared to those treated with bupropion[183].

183. Grunebaum MF, Ellis SP, Duan N, Burke AK, Oquendo MA, Mann JJ. Pilot randomized clinical trial of an SSRI vs bupropion: Effects on suicidal behavior, ideation, and mood in major depression. Neuropsychopharmacology. 2012;37(3):697-706.

The Assessment and Management of Risk for Suicide Working Group, 2013 [5].

Department of Veterans Affairs; Department of Defense

VA/DoD CLINICAL PRACTICE GUIDELINE FOR ASSESSMENT AND MANAGEMENT OF PATIENTS AT RISK FOR SUICIDE

Version 1.0 – June 2013

Leitlinienorganisation/Fragestellung

The intent of the guidelines is to:

Reduce current unwarranted practice variation and provide facilities with a structured framework to help improve patient outcomes (prevent suicide and other forms of suicidal self-directed violent behavior)

Provide evidence-based recommendations to assist providers and their patients in the decision-making process

[…]

Target Population:

Adult patients (18 years or older) with Suicidal Self-Directed Violent (SDV) behavior or related suicidal ideation (identified as being at risk for suicide) who are managed in the VA and DoD healthcare clinical settings. The population at risk includes patients who have suicidal ideation with or without an established diagnosis of a Mental or Substance Use Disorder; and patients with any level of risk for suicide ranging from thoughts of about death or suicide to SDV behavior or suicide attempt.

Methodik

Grundlage der Leitlinie

The Offices of Quality Safety and Values and Patient Care Services of the VA, and the Army Medical Command of the DoD identified clinical leaders to champion the guideline development process. During a preplanning conference meeting, the clinical leaders defined the scope of the guideline and identified a group of clinical experts from the VA and DoD to form the Assessment and Management of Risk for Suicide Working Group (WG).

The WG's participants were drawn from the fields of primary care, psychiatry, psychology, pharmacology, nursing, and social work.

Face-to-face meeting to reach consensus about the guideline algorithm and evidence-based recommendations and to prepare a draft update document

Informal consensus within the WG sufficient to formulate recommendations based on the best evidence and or experience of the clinical experts. In areas where this approach did not lead to conclusion, the facilitator used a structured discussion format (i.e. a modified nominal group process) to expedite the process and reach consensus based on the collective experience of the group.

Recherche/Suchzeitraum:

PubMed, PsycINFO, the Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled Trials, and covered the period from January 2005 to November 18, 2011

LoE

Table A-1: Level of Evidence (LE)	
I	At least one properly done RCT
II-1	Well-designed controlled trial without randomization
II-2	Well-designed cohort or case-control analytic study, preferably from more than one source
II-3	Multiple time series evidence with/without intervention, dramatic results of uncontrolled experiment
III	Opinion of respected authorities, descriptive studies, case reports, and expert committees

Table A-2: Overall Quality [QE]	
Good	High grade evidence (I or II-1) directly linked to health outcome
Fair	High grade evidence (I or II-1) linked to intermediate outcome; or Moderate grade evidence (II-2 or II-3) directly linked to health outcome
Poor	Level III evidence or no linkage of evidence to health outcome

GoR

Table A-3: Net Effect of the Intervention [NB]	
Substantial	More than a small relative impact on a frequent condition with a substantial burden of suffering; *or* A large impact on an infrequent condition with a significant impact on the individual patient level.
Moderate	A small relative impact on a frequent condition with a substantial burden of suffering; *or* A moderate impact on an infrequent condition with a significant impact on the individual patient level.
Small	A negligible relative impact on a frequent condition with a substantial burden of suffering; *or* A small impact on an infrequent condition with a significant impact at the individual patient level.
Zero or Negative	Negative impact on patients; *or* No relative impact on either a frequent condition with a substantial burden of suffering, or an infrequent condition with a significant impact on the individual patient level.

Table A-4: Final Grade of Recommendation [SR]				
	The Net Benefit of the Intervention			
Certainty in the Quality of Evidence	Substantial	Moderate	Small	Zero or Negative
High	A	B	C	D
Moderate	B	B	C	D
Low	I	I	I	I

Modified according to USPSTF Update (Sawaya et al.,, 2007)

A	A strong recommendation that the clinicians provide the intervention to eligible patients. *Good evidence was found that the intervention improves important health outcomes and concludes that benefits substantially outweigh harm.*
B	A recommendation that clinicians provide (the service) to eligible patients. *At least fair evidence was found that the intervention improves health outcomes and concludes that benefits outweigh harm.*
C	No recommendation for or against the routine provision of the intervention is made. *At least fair evidence was found that the intervention can improve health outcomes, but concludes that the balance of benefits and harms is too close to justify a general recommendation.*
D	Recommendation is made against routinely providing the intervention to asymptomatic patients. *At least fair evidence was found that the intervention is ineffective or that harms outweigh benefits.*
I	The conclusion is that the evidence is insufficient to recommend for or against routinely providing the intervention. *Evidence that the intervention is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.*

Sonstige methodische Hinweise

Keine direkte Verknüpfung von Empfehlung und Literatur, Evidenz für jede Empfehlung wird separat diskutiert

Empfehlungen

M. Pharmacological Treatment to Reduce Risk for Suicide in Patients with Mental Disorders

When self-harm behavior or suicide risk is attributable to a psychiatric illness, that illness needs to be identified and treated and the treatment plan modified when appropriate to specifically address the risk of suicide.

RECOMMENDATIONS

1. Pharmacological intervention may be markedly helpful in managing underlying mental disorders and the danger of repeated or more dangerous self-directed violence.
2. All medications (prescription drugs, over-the-counter medications, and supplements [e.g., herbal remedies]) used by patients at risk for suicide should be reviewed to assure effective and safe treatment without adverse drug interactions.
3. When prescribing drugs to people who self-harm, consider the toxicity of prescribed drugs in overdose and limit the quantity dispensed or available, and/or identify another person to be responsible for securing access to medications. The need for follow-up and monitoring for adverse events should also be considered.

M2. Use of Antipsychotics to Prevent Suicide in a Patient with a Non-Psychotic Disorder

RECOMMENDATIONS

1. There is no evidence that antipsychotics provide additional benefit in reducing the risk of suicidal thinking or behavior in patients with co-occurring psychiatric disorders. Treatment for the psychiatric disorder should be optimized according to evidence-based guidelines for the respective disorder.
2. Patients who are treated with antipsychotics should be monitored for changes in behavior and emergence of suicidal thoughts during the initiation phase of treatment or after any change in dosage.
3. When prescribing antipsychotics in patients at risk for suicide pay attention to the risk of overdose and limit the amount of medication dispensed and refilled.

M3. Use of Lithium for Reducing Suicide in Patients with Unipolar Depressive Disorder

RECOMMENDATIONS

1. Lithium augmentation should be considered for patients diagnosed with unipolar depressive disorder who have had a partial response to an antidepressant and for those with recurrent episodes who are at high risk for suicidal behavior, provided they do not have a contraindication to lithium use and the potential benefits outweigh the risks. [C]
2. Lithium should be avoided or used in caution in patients with impaired renal function, those taking concurrent medications that increase or decrease lithium concentrations or those with other risk factors for lithium toxicity.
3. When prescribing lithium to patients at risk for suicide, it is important to pay attention to the risk of overdose by limiting the amount of lithium dispensed and the form in which it is provided.

EVIDENCE TABLE

	Evidence	Source	LE	QE	NB	SR
1	Lithium for patients diagnosed with recurrent major depression disorder	Cipriani et al., 2009 Guzzetta et al., 2007	I II	Mod	Small	C

LE=Level of Evidence; QE=Quality of Evidence; NB=Net Benefit; SR=Strength of Recommendation (See Appendix A)

N. Electroconvulsive Therapy (ECT) in the Prevention of Suicide

RECOMMENDATIONS:

1. ECT is recommended as a treatment option for severe episodes of major depression that are accompanied by suicidal thoughts or behaviors indicating imminent risk for suicide, considering patient preferences.
2. Under certain clinical circumstances and, considering patient preference, ECT may also be considered to treat suicidal patients with schizophrenia, schizoaffective disorder, or mixed or manic episodes of bipolar disorder.
3. The decision of whether to initiate ECT treatment should follow evidence-based recommendation for the specific disorder, and be based on documented assessment of the risks and potential benefits to the individual, including: the risks associated with the anesthetic; current co-morbidities; anticipated adverse events; and the risks of not having treatment.
4. Since there is no evidence of a long-term reduction of suicide risk with ECT, continuation or maintenance treatment with pharmacotherapy or with ECT is recommended after an acute ECT course.

5. ECT should be performed by experts in centers that are properly equipped and experienced in the treatment.
6. In general, the following conditions increase the indications to use ECT:
    a. A history of prior good response to ECT
    b. Need for rapid, definitive treatment response
    c. Risks of other treatments outweigh the risks of ECT
    d. History of poor response to medication treatment
    e. Intolerable side effects to medication treatments
    f. Patient preference.
7. The risk-versus-benefits ratio must be considered in patients with relative contraindications such as [B]:
    a. Space occupying lesions
    b. Elevated intracranial pressure
    c. Cardiovascular problems to include recent myocardial infarction, severe cardiac ischemic disease, or profound hypertensive illness.
    d. Degenerative skeletal disease
    e. Monamine Oxidase Inhibitors should be discontinued two weeks prior to ECT to prevent possible hypertensive crisis
    f. Lithium: patients may develop neurotoxic syndrome with confusion, disorientation, and unresponsiveness
    g. Retinal detachment
    h. Pheochromocytoma
    i. High Anesthesia Risk: American Society of Anesthesiologists level 4 or 5.

There is insufficient evidence to demonstrate enduring effects on suicide rates after short-term ECT. There is some evidence to suggest rapid short-term benefits in reducing suicidal ideation and intent in severe depression. Similar to the situation with antidepressant therapy, there is still very little information arising from systematically applied and evaluated long-term treatment with ECT comparable to the data available for maintenance treatment with lithium and clozapine, and it is not reasonable to expect long-term effects on suicide risk from time-limited treatment interventions of any kind.

3.5 Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

Es wurden keine Quellen identifiziert.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 9 of 12, September 2018) am 11.09.2018

#	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

Systematic Reviews in Medline (PubMed) am 17.09.2018

#	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 ("2013/09/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 17.09.2018

#	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*[ti])*
6	(((#5) AND ("2013/09/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))

Referenzen

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3. **Lam RW, Kennedy SH, Parikh SV, MacQueen GM, Milev RV, Ravindran AV.** Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Introduction and Methods. Can J Psychiatry 2016;61(9):506-509.

4. **Malhi GS, Bassett D, Boyce P, Bryant R, Fitzgerald PB, Fritz K, et al.** Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Aust N Z J Psychiatry 2015;49(12):1087-1206.

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7. **National Institute for Health and Care Excellence (NICE).** Depression: the treatment and management of depresion in adults (updated edition) [online]. April 2018. London (GBR): NICE; 2009. [Zugriff: 17.09.2018]. (Clinical guideline; Band 90). URL: https://www.nice.org.uk/guidance/cg90#.

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