Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2015-05-01-D-162 Vortioxetin

Stand: März 2014

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

Vortioxetin **[Major 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.	Agomelatin, Amitriptylin, Amitriptylinoxid, Bupropion, Citalopram, Clomipramin, Dosulepin, Doxepin, Duloxetin, Escitalopram, Fluoxetin, Fluvoxamin, Imipramin, Johanniskraut, Lithium, Maprotilin, Mianserin, Mirtazapin, Moclobemid, Nortriptylin, Paroxetin, Reboxetin, Sertralin, Tianeptin, Trazodon, Trimipramin, Venlafaxin
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Psychotherapeutische Verfahren gemäß Psychotherapie-Richtlinie
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Verordnungsauschluss Reboxetin 12.Jan.2010 Beschluss Festbetragsgruppenbildung, Aktualisierung von Vergleichsgrößen Citalopram und Escitalopram 17.Feb. 2011
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

Vortioxetin **N06AX26** **Brintellix®**	Anwendungsgebiet laut Beratungsanforderung: „Brintellix wird angewendet zur Behandlung von Episoden einer Major Depression bei Erwachsenen “
Zu bewertendes Arzneimittel:	
Wirkstoff ATC-Code Handelsname®	**Anwendungsgebiet** (Text aus Fachinformation)
Imipramin N06AA02 Generisch	Depressive Syndrome unabhängig von ihrer nosologischen Einordnung.
Clomipramin N06AA04 Generisch	Depressive Syndrome unabhängig von ihrer nosologischen Zuordnung.
Trimipramin N06AA06 Generisch	Depressive Erkrankungen mit den Leitsymptomen Schlafstörungen, Angst und innere Unruhe.
Amitriptylin N06AA09 Generisch	Depressive Erkrankungen.
Nortriptylin N06AA10 Nortrilen®	Depressive Zustandsbilder jeder Ätiologie, vor allem, wenn sie durch vitale Hemmung und Antriebsverarmung gekennzeichnet sind.
Doxepin N06AA12 Generisch	Depressive Erkrankungen.
Dosulepin N06AA16 Idom®	Depressive Erkrankungen.
Maprotilin N06AA21 Generisch	Depressive Erkrankung.
Amitriptylinoxid N06AA25	Behandlung depressiver Erkrankungen.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Generisch	
Fluoxetin N06AB03 Generisch	Episoden einer Major Depression.
Citalopram N06AB04 Generisch	Behandlung depressiver Erkrankungen (Episoden einer Major Depression).
Paroxetin N06AB05 Generisch	Behandlung von depressiven Erkrankungen (Episoden einer Major Depression).
Sertralin N06AB06 Generisch	Episoden einer Major Depression.
Fluvoxamin N06AB08 Generisch	Episoden einer Major Depression.
Escitalopram N06AB10 Cipralex®	Behandlung von Episoden einer Major Depression.
Tranylcypromin N06AF04 Jatrosom®	Depressive Syndrome unabhängig ihrer nosologischen Einordnung.
Moclobemid N06AG02 Generisch	Behandlung von Episoden einer Major Depression.
Mianserin N06AX03 Generisch	Depressive Störungen.
Trazodon N06AX05 Generisch	Depressive Erkrankungen, unabhängig von ihrer nosologischen Zuordnung.
Mirtazapin N06AX11 Generisch	Episoden einer Major Depression.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Bupropion N06AX12 Elontril®	Behandlung von Episoden einer depressiven Erkrankung (Episoden einer Major Depression).
Tianeptin N06AX14 Tianeurax®	Zur Behandlung von Depressionen bei Erwachsenen.
Venlafaxin N06AX16 Generisch	Behandlung von Episoden einer Major Depression.
Reboxetin N06AX18 Solvex®	Reboxetin ist für die Behandlung akuter depressiver Erkrankungen/Episoden einer Major Depression bestimmt. Die Behandlung sollte bei Patienten, die initial auf Solvex ® 4mg Tabletten angesprochen haben, zur Aufrechterhaltung der klinischen Besserung fortgeführt werden.
Duloxetin N06AX21 Cymbalta®	Zur Behandlung von depressiven Erkrankungen (Major Depression).
Agomelatin N06AX22 Valdoxan®	Behandlung von Episoden einer Major Depression bei Erwachsenen.
Lithium N05AN01 Hypnorex®	Bei bestimmten akuten Depressionen, z. B. bei Therapieresistenz oder Unverträglichkeit von Antidepressiva.
Johanniskraut N06AP01 Jarsin Rx 300 mg®	Mittelschwere depressive Episoden.

Quellen: atd-Arzneimitteldatenbank, Fachinformationen (Stand: März 2014)

Synoptische Evidenzübersicht zur Ermittlung der zweckmäßigen Vergleichstherapie:

Inhalt

Indikation für die Recherche:
Behandlung von Episoden einer Major Depression bei Erwachsenen.

Berücksichtigte Wirkstoffe/Therapien:
Siehe Liste der in Deutschland zugelassenen Therapieoptionen

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation ***„Depression bei Erwachsenen“*** durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am ***04.03.2014*** abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (einschl. NHS CRD-Datenbanken), MEDLINE (PubMed), Leitlinien.de (ÄZQ), AWMF, GIN, NGC, TRIP, DAHTA, NIHR HSC. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Es wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab **984** Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Davon wurden **130** Quellen eingeschlossen. Insgesamt ergab dies **56** Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Leitlinien

DGPPN, 2012: Unipolare Depression. Langfassung (National Versorgungsleitlinie/S3-Leitlinie)	**Pharmakotherapie** • 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. Hält die Symptomatik nach einer Kontrolle nach spätestens 14 Tagen noch an oder hat sie sich verschlechtert, soll mit dem Patienten über die Einleitung einer spezifischen Therapie entschieden werden. (LoE: 0) • Antidepressiva sollten nicht generell zur Erstbehandlung bei leichten depressiven Episoden eingesetzt werden, sondern allenfalls unter besonders kritischer Abwägung des Nutzen-Risiko-Verhältnisses. (LoE: B) • Zur Behandlung einer akuten mittelgradigen depressiven Episode soll Patienten eine medikamentöse Therapie mit einem Antidepressivum angeboten werden. (LoE: A) • Bei akuten schweren depressiven Episoden soll eine Kombinationsbehandlung mit medikamentöser Therapie und Psychotherapie angeboten werden. (LoE: A) • 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: 0). 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: B) **Therapiebeginn** • Bei jedem Patienten 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. (LoE: Statement) • 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. (LoE: Statement) **Effektivität psychotherapeutischer Verfahren in der Akuttherapie** <u>Empfehlungen zur psychotherapeutischen Akutbehandlung</u> • 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. Hält die Symptomatik nach einer Kontrolle nach spätestens 14 Tagen noch an oder hat sie sich verschlechtert, soll mit dem Patienten über die Einleitung einer spezifischen Therapie entschieden werden. (LoE: B) • Zur Behandlung akuter leichter bis mittelschwerer depressiver Episoden soll

	eine Psychotherapie angeboten werden. (LoE: A) • Bei akuten schweren Depressionen soll eine Kombinationsbehandlung mit medikamentöser Therapie und Psychotherapie angeboten werden. (LoE: A) • Wenn ein alleiniges Behandlungsverfahren in Betracht gezogen wird, soll bei ambulant behandelbaren Patienten mit akuten mittelschweren bis schweren depressiven Episoden eine alleinige Psychotherapie gleichwertig zu einer alleinigen medikamentösen Therapie angeboten werden. (LoE: A) • Depressive Patienten mit psychotischen Merkmalen sollten in jedem Falle eine medikamentöse Therapie erhalten. (LoE: Statement) **Nichtmedikamentöse somatische Therapieverfahren** <u>Elektrokonvulsive Therapie</u> • EKT soll bei schweren, therapieresistenten depressiven Episoden als Behandlungsalternative in Betracht gezogen werden. (LoE: A) <u>Wachtherapie (Schlafentzugstherapie)</u> • 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: B) <u>Lichttherapie</u> • Lichttherapie soll als Behandlungsform bei Patienten mit leicht- bis mittelgradigen Episoden rezidivierender depressiver Störungen, die einem saisonalen Muster folgen, erwogen werden. (LoE: A) • Mit Lichttherapie behandelte Patienten mit saisonal abhängiger depressiver Episode, die auf diese Therapieform ansprechen, können die Lichttherapie den gesamten Winter über fortsetzen. (LoE: 0) <u>Körperliches Training</u> • Körperliches Training kann aus klinischer Erfahrung heraus empfohlen werden, um das Wohlbefinden zu steigern und depressive Symptome zu lindern. (LoE: KKP) **Neuere nichtpharmakologische therapeutische Möglichkeiten** <u>Vagus-Nerv-Stimulation</u> • Für die Repetitive Transkranielle Magnetstimulation (rTMS) und die Vagus-Nerv-Stimulation (VNS), neue somatische Therapieverfahren bei Depression, gibt es noch zu wenig Evidenz, um Empfehlungen für ihre allgemeine klinische Nützlichkeit und Anwendbarkeit aussprechen zu können. (LoE: Statment). **Maßnahmen bei Nichtansprechen** • Spricht ein Patient nach 3-4 Wochen nicht auf eine Antidepressivamonotherapie an, sollten zunächst Ursachen für diesen Verlauf evaluiert werden. Zu diesen Ursachen gehören gegebenenfalls die mangelnde Mitarbeit des Patienten, eine nicht angemessene Dosis und ein zu niedriger Serumspiegel. (LoE: 0) • 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: 0) • Ein Versuch zur Wirkungsverstärkung (Augmentation) mit Lithium sollte vom erfahrenen Arzt bei Patienten erwogen werden, deren Depression auf

	Antidepressiva nicht angesprochen hat. (LoE: B) • Wenn bei einem Patienten 2-4 Wochen nach Erreichen wirksamer Lithiumspiegel keine Wirkung festzustellen ist, sollte Lithium wieder abgesetzt werden. (LoE: KKP) • Patienten, die gut auf ein Antidepressivum mit Lithium-Augmentation ansprachen, sollten unter diesem Regime für mindestens 6 Monate bleiben. (LoE: B) • Die Augmentation von Antidepressiva mittels Carbamazepin, Lamotrigin, Pindolol, Valproat, Dopaminagonisten, Psychostimulanzien, Schilddrüsen- oder anderen Hormonen wird als Routineeinsatz bei therapieresistenter Depression nicht empfohlen. (LoE: 0) • Beim Wechsel zwischen Antidepressiva sollten wegen möglicher Wechselwirkungen eine schrittweise Aufdosierung des neuen und ein ausschleichendes Absetzen des alten Antidepressivums erfolgen. (LoE: B) • Der Wechsel des Antidepressivums ist bei Nichtansprechen nicht die Behandlungsalternative erster Wahl. Jeder Wechsel sollte daher sorgfältig geprüft werden. (LoE: B) • 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. (LoE: Statement) • 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 Kombination wurde in mehreren randomisierten und doppelblinden Studien gezeigt, dass sie wirksamer ist als die Monotherapie mit nur einem der Wirkstoffe. (LoE: Statement) • Bei schweren und rezidivierenden sowie chronischen Depressionen, Dysthymie und Double Depression sollte die Indikation zur Kombinationsbehandlung aus Pharmakotherapie und geeigneter Psychotherapie vorrangig vor einer alleinigen Psychotherapie oder Pharmakotherapie geprüft werden. (LoE: B) • EKT soll bei schweren, therapieresistenten depressiven Episoden als Behandlungsalternative in Betracht gezogen werden. (LoE: A) • EKT kann auch zur Erhaltungstherapie eingesetzt werden bei Patienten, die während einer Krankheitsepisode auf EKT angesprochen haben; nicht angesprochen haben auf eine andere leitliniengerechte antidepressive Therapie; psychotische Merkmale aufweisen oder eine entsprechende Präferenz haben. (LoE: 0)
NICE, 2009: Depression in adults. The treatment and management of depression in adults	**Low-intensity psychosocial interventions** For people with persistent subthreshold depressive symptoms or mild to moderate depression, consider offering one or more of the following interventions, guided by the person's preference: • individual guided self-help based on the principles of cognitive behavioral therapy (CBT) • computerised cognitive behavioral therapy (CCBT) • a structured group physical activity programme. **Drug treatment** Do not use antidepressants routinely to treat persistent subthreshold depressive symptoms or mild depression because the risk–benefit ratio is poor, but consider them for people with:

	• a past history of moderate or severe depression **or** • initial presentation of subthreshold depressive symptoms that have been present for a long period (typically at least 2 years) **or** • subthreshold depressive symptoms or mild depression that persist(s) after other interventions. For people with persistent subthreshold depressive symptoms or mild to moderate depression who have not benefited from a low-intensity psychosocial intervention, discuss the relative merits of different interventions with the person and provide: • an antidepressant (normally a selective serotonin reuptake inhibitor [SSRI]) **or** • a high-intensity psychological intervention, normally one of the following options: o CBT o interpersonal therapy (IPT) o behavioural activation (but note that the evidence is less robust than for CBT or IPT) o behavioural couples therapy for people who have a regular partner and where the relationship may contribute to the development or maintenance of depression, or where involving the partner is considered to be of potential therapeutic benefit. For people with moderate or severe depression, provide a combination of antidepressant medication and a high-intensity psychological intervention (CBT or IPT). The choice of intervention should be influenced by the: • duration of the episode of depression and the trajectory of symptoms • previous course of depression and response to treatment • likelihood of adherence to treatment and any potential adverse effects person's treatment preference and priorities. For people with depression who decline an antidepressant, CBT, IPT, behavioural activation and behavioural couples therapy, consider: • counselling for people with persistent subthreshold depressive symptoms or mild to moderate depression • short-term psychodynamic psychotherapy for people with mild to moderate depression. **Antidepressant drugs** Discuss antidepressant treatment options with the person with depression, covering: • the choice of antidepressant, including any anticipated adverse events, for example side effects and discontinuation symptoms (see 1.9.2.1), and potential interactions with concomitant medication or physical health problems • their perception of the efficacy and tolerability of any antidepressants they have previously taken. When an antidepressant is to be prescribed, it should normally be an SSRI in a generic form because SSRIs are equally effective as other antidepressants and have a favorable risk–benefit ratio. Also take the following into account: • SSRIs are associated with an increased risk of bleeding, especially in older people or in people taking other drugs that have the potential to damage the gastrointestinal mucosa or interfere with clotting. In particular, consider prescribing a gastroprotective drug in older people who are taking non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin. • Fluoxetine, fluvoxamine and paroxetine are associated with a higher propensity for drug interactions than other SSRIs. • Paroxetine is associated with a higher incidence of discontinuation symptoms than other SSRIs. 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. When prescribing drugs other than SSRIs, take the following into account: • The increased likelihood of the person stopping treatment because of side effects (and the consequent need to increase the dose gradually) with venlafaxine, duloxetine and TCAs. • The specific cautions, contraindications and monitoring requirements for some drugs. For example: o the potential for higher doses of venlafaxine to exacerbate cardiac arrhythmias and the need to monitor the person's blood pressure o the possible exacerbation of hypertension with venlafaxine and duloxetine o the potential for postural hypotension and arrhythmias with TCAs o the need for haematological monitoring with mianserin in elderly people. • Non-reversible monoamine oxidase inhibitors (MAOIs), such as phenelzine, should normally be prescribed only by specialist mental health professionals. • Dosulepin should not be prescribed.
NZGG, 2008: Identification of and Management of in Primary Care Common Mental Disorders Depression	**Management of depression in adults** • An adult with serious suicidal intent, psychotic symptoms or severe and persistent self-neglect should be referred immediately to secondary care mental health services (LoE: C) • First-line treatment for an adult with mild depression is active support, advice on exercise and self-management, and referral to psychosocial helping agencies as required (eg, relationship counselling) (LoE: C) • First-line treatment for an adult with moderate depression is either a selective serotonin reuptake inhibitor (SSRI) or a psychological therapy (eg, 6–8 sessions of problem-solving therapy or cognitive behavioural therapy [CBT] over 10–12 weeks) (LoE: B) • For an adult presenting initially with severe depression, the practitioner should consider a combination of antidepressant medication with a structured psychological intervention (eg, CBT or interpersonal psychotherapy [IPT], 16–20 sessions) (LoE: B) • An adult starting antidepressant treatment who is considered at increased risk of suicide or is younger than 30 years should be followed up at 1 week and monitored 1–2 weekly, preferably face-toface, until the risk is no longer considered significant, then at least 2 weekly until there is clear improvement (LoE: C) • An adult starting antidepressant treatment who is not considered at increased risk of suicide should be reviewed by the health practitioner within 1–2 weeks and monitored at least 2 weekly until there is clear improvement (LoE: C) • If an adult on antidepressant medication has had only a partial response after 3–4 weeks, consider increasing the dose (LoE: C) • If an adult on antidepressant medication has not responded to treatment by 4–6 weeks, review the treatment plan and consider either increasing the dose, changing the antidepressant, or changing or adding a psychological therapy (LoE: C) • An adult being treated for depression should be actively monitored and supported (eg, by phone, text, email or face-to-face) by an appropriately trained member of the primary care team, informed by clear treatment protocols (LoE: B) • Practitioners should consider the use of a tool such as the Patient Health Questionnaire for Depression (PHQ-9) to assist in the monitoring of treatment response in an adult with depression (LoE: B)

	• If another health practitioner delivers psychotherapy to an adult with depression, the primary care team should be in regular communication about the individual's progress (LoE: C) • An adult with depression who is treatment resistant should be referred urgently to secondary care mental health services while continuing treatment. Treatment resistance is defined as an unsatisfactory response after adequate trial of two antidepressants (with or without psychological therapy) (LoE: C) • An adult with depression who is responding to antidepressant treatment should normally continue to take the antidepressant for at least 6 months after remission of an episode of depression in order to reduce the risk of relapse (LoE: B) ***Hinweis: Keine Angabe des LoE bei den folgenden Empfehlungen!*** <u>Persistent subtreshold depressive symptoms for mild ro moderate depression with inadequate response to initial interventions, and moderate and severe depression</u> **Treatment options:** For people with persistent subthreshold depressive symptoms or mild to moderate depression who have not benefited from a low-intensity psychosocial intervention, discuss the relative merits of different interventions with the person and provide: • an antidepressant (normally a selective serotonin reuptake inhibitor [SSRI]) or • a high-intensity psychological intervention, normally one of the following options: o CBT o interpersonal therapy (IPT) o behavioural activation (but note that the evidence is less robust than for CBT or IPT) o behavioural couples therapy for people who have a regular partner and where the relationship may contribute to the development or maintenance of depression, or where involving the partner is considered to be of potential therapeutic benefit. For people with moderate or severe depression, provide a combination of antidepressant medication and a high-intensity psychological intervention (CBT or IPT). The choice of intervention should be influenced by the: • duration of the episode of depression and the trajectory of symptoms • previous course of depression and response to treatment • likelihood of adherence to treatment and any potential adverse effects • person's treatment preference and priorities. For people with depression who decline an antidepressant, CBT, IPT, behavioural activation and behavioural couples therapy, consider: • counselling for people with persistent subthreshold depressive symptoms or mild to moderate depression • short-term psychodynamic psychotherapy for people with mild to moderate depression. Discuss with the person the uncertainty of the effectiveness of counseling and psychodynamic psychotherapy in treating depression. **<u>Sequencing treatments after initial inadequate response</u>** **Drug treatments:** 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 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. *Switching antidepressants* 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. 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. 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 syndrome • from a non-reversible MAOI: a 2-week washout period is required (other antidepressants should not be prescribed routinely during this period). *Combining and augmenting medications* 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. 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.

	When prescribing lithium: • monitor renal and thyroid function before treatment and every 6 months during treatment (more often if there is evidence of renal impairment) • consider ECG monitoring in people with depression who are at high risk of cardiovascular disease • monitor serum lithium levels 1 week after initiation and each dose change until stable, and every 3 months thereafter. When prescribing an antipsychotic, monitor weight, lipid and glucose levels, and side effects (for example, extrapyramidal side effects and prolactin-related side effects with risperidone). 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. *Combined psychological and drug treatment* For a person whose depression has not responded to either pharmacological or psychological interventions, consider combining antidepressant medication with CBT. *Referral* 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. For people with depression who are at significant risk of relapse or have a history of recurrent depression, discuss with the person treatments to reduce the risk of recurrence, including continuing medication, augmentation of medication or psychological treatment (CBT). Treatment choice should be influenced by: • previous treatment history, including the consequences of a relapse, residual symptoms, response to previous treatment and any discontinuation symptoms • the person's preference. People with depression who are considered to be at significant risk of relapse (including those who have relapsed despite antidepressant treatment or who are unable or choose not to continue antidepressant treatment) or who have residual symptoms, should be offered one of the following psychological interventions: • individual CBT for people who have relapsed despite antidepressant medication and for people with a significant history of depression and residual symptoms despite treatment • mindfulness-based cognitive therapy for people who are currently well but have experienced three or more previous episodes of depression.

Working Group on the Management of Major Depression in Adults (Spanish SHN), 2008: Clinical Practice Guideline on the Management of Major Depression in Adults	**Pharmacological treatment** A — Antidepressant drugs represent a first line of treatment for moderate or severe depression. ✓ — For mild depression, other therapeutic strategies can be considered before antidepressant drugs. D — The use of drugs is recommended for those patients with mild depression and a history of moderate or severe episodes of depression. D — The use of drugs is recommended for mild depression when other medical illnesses or associated comorbidity may be present. ✓ — It is advisable to set up an appointment within 15 days for any patient with depression who does not receive pharmacological treatment. A — SSRIs are recommended as drugs of first choice in the treatment of major depression. B — In the event that an SSRI drug is not well-tolerated due to the appearance of adverse effects, it should be switched to another drug of the same group. A — An SSRI should be prescribed for patients who may receive treatment with any tricyclic antidepressant and who do not tolerate it. ✓ — TCAs are an alternative to SSRIs if a patient has not tolerated at least two drugs from this group or is allergic to them. ✓ — New drugs could be used in the event of intolerance to SSRIs, thereby using the profile of their adverse effects as a guideline.

B	Specific patient profiles could warrant different drugs, thereby using the adverse effects rather than their efficacy as a guideline.
A	Venlafaxine should be considered as a second line of treatment in patients with major depression.
✓	Before starting antidepression treatment, a healthcare professional should adequately inform the patient about the expected benefits; the frequent, infrequent and patient-specific side effects that could arise, in both the short and the long-term; and especially about the duration of the treatment.
✓	It is especially advisable to inform about a possible delay in the therapeutic effect of antidepressants.
✓	Patients receiving antidepressant drug treatment must be closely monitored, at least during the first 4 weeks.
✓	All patients who show moderate major depression and who are treated with antidepressant drugs must be assessed again before 15 days after initiating treatment.
✓	All patients who show severe major depression and who receive outpatient treatment with antidepressant drugs must be assessed again before 8 days after initiating treatment.
A	Pharmacological treatment must be maintained in all patients for at least 6 months after remission.
B	In patients with any previous episode or the presence of residual symptoms, the treatment must be maintained for at least 12 months after remission.
✓	In patients with more than 2 previous episodes, the treatment must be maintained for at least 24 months after remission.
B	The dose of the drug used during the maintenance phase must be similar to the dose used to achieve remission.
✓	In patients with a partial response at the third or fourth week of treatment, it is advisable: - To wait for the clinical evolution until week eight. - To increase the dose of the drug up to the maximum therapeutic dose.
✓	For a patient who does not improve with the initial drug treatment for depression, it is advisable: - To revise the diagnosis of depressive disorder. - To verify that the treatment is being followed. - To confirm that the antidepressant is being taken at the right time and dose.
B	If the patient does not improve at the third or fourth week, any of the following strategies could be followed: - Switching from an antidepressant to any family, including another serotonergic. - Combining antidepressants. - Augmenting the initiated treatment with lithium or triiodothyronine.
B	It is not advisable to increase the SSRI dose if there is no response after 3 weeks of treatment.
C	The association of SSRI with mirtazapine or mianserin could also be a recommendable option, but thereby taking into account the possibility of greater adverse effects.
B	There is insufficient information available to recommend an increase in the dose of tricyclic antidepressants in non-responders.
✓	In the event of resistance to various treatments according to the aforementioned guidelines, assess the use of MAOIs.
✓	There is insufficient data for recommending augmentation with valproate, carbamazepine, lamotrigine, gabapentin or topiramate, pindolol, benzodiazepines, buspirone, methylphenidate or atypical antipsychotics.

Psychotherapy:

✓	Psychological interventions should be provided by professionals who have experience at managing depression and who are experts in the applied therapy. This is especially important in the most severe cases.
B	In mild and moderate depression, specific and brief psychological treatment (such as problem-solving therapy, cognitive behavioural therapy or counselling) in 6 to 8 sessions during 10-12 weeks should be considered.
B	The preferred psychological treatment for moderate, severe or resistant depression is cognitive behavioural therapy. Interpersonal therapy can be considered as a reasonable alternative.
B	For moderate and severe depression, suitable psychological treatment should include 16 to 20 sessions during at least five months.
B	For moderate depression, either antidepressant drug treatment or suitable psychological intervention can be recommended.
B	Cognitive behavioural therapy should be offered to patients with moderate or severe depression who reject drug treatment or for whom avoiding the secondary effects of antidepressants is a clinical priority or who express that personal preference.
B	Couples therapy should be considered, if applicable, in the event that a suitable response is not obtained with previous individual intervention.
B	Cognitive behavioural therapy should be considered for patients who have not had a suitable response to other interventions or who may have a prior history of relapses or residual symptoms, despite treatment.
B	Cognitive behavioural therapy should be considered for patients who have recurrent depression and who have relapsed despite antidepressant treatment or who express a preference for psychological treatment.
A	For patients whose depression is resistant to pharmacological treatment and/or who have multiple episodes of recurrence, a combination of antidepressants and cognitive behavioural therapy should be offered.
A	A combination of cognitive behavioural therapy and antidepressant medication should be offered to patients with chronic depression.
C	Whenever cognitive behavioural therapy is applied to more severe patients, the techniques based on behavioural activation should be given priority.
C	Psychological interventions other than the aforementioned could be useful for dealing with comorbidity or the complexity of the family relationships frequently associated with the depressive disorder.

<table>
<tr><td></td><td>Other Treatments:
<table>
<tr><td>A</td><td>Electroconvulsive therapy should be considered as a therapeutic alternative in adults with severe major depression.</td></tr>
<tr><td>✓</td><td>ECT is especially indicated for patients with severe major depression (with a high risk of suicide or severe physical impairment) in resistant depression and by informed choice of the patient.</td></tr>
<tr><td>✓</td><td>In general, guided self-help is not recommended for patients with severe major depression.</td></tr>
<tr><td>B</td><td>However, for patients with mild or moderate depression, professionals could consider recommending guided self-help programmes based on cognitive behavioural therapy.</td></tr>
<tr><td>✓</td><td>Participation in support groups is not considered an effective treatment measure in patients with the major depression disorder, either alone or combined with other therapeutic measures.</td></tr>
<tr><td>C</td><td>Programmes of structured and supervised exercise of moderate intensity, with a frequency of 2-3 times per week, with a duration of 40-45 minutes and for a period of 10 to 12 weeks should be recommended to patients with mild-moderate depression.</td></tr>
<tr><td>✓</td><td>The existing scientific evidence does not allow recommending the use of acupuncture as a treatment for major depression.</td></tr>
<tr><td>B</td><td>The use of St John's Wort is not recommended as a treatment option for patients with major depression.</td></tr>
<tr><td>✓</td><td>Health professionals should inform patients who consume it about the possible risks and benefits.</td></tr>
</table></td></tr>
<tr><td>APA, 2010: Practice guideline for the treatment of patients with major depressive disorder</td><td>Acute phase:
<u>Choice of an initial treatment modality</u>
• Acute phase treatment may include pharmacotherapy, depression-focused psychotherapy, the combination of medications and psychotherapy, or other somatic therapies such as electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), or light therapy, as described in the sections that follow. Selection of an initial treatment modality should be influenced by clinical features (e.g., severity of symptoms, presence of co-occurring disorders or psychosocial stressors) as well as other factors (e.g., patient preference, prior treatment experiences) [LoE: I]
<u>Pharmacotherapy</u>
• An antidepressant medication is recommended as an initial treatment choice for patients with mild to moderate major depressive disorder [LoE: I] and definitely should be provided for those with severe major depressive disorder unless ECT is planned [LoE: I]
• Because the effectiveness of antidepressant medications is generally comparable between classes and within classes of medications, the initial selection of an antidepressant medication will largely be based on the anticipated side effects, the safety or tolerability of these side effects for the individual patient, pharmacological properties of the medication (e.g., half-life, actions on cytochrome P450 enzymes, other drug interactions), and additional factors such as medication response in prior episodes, cost, and patient preference [LoE: I]
• For most patients, a selective serotonin reuptake inhibitor (SSRI), serotonin norepinephrine reuptake inhibitor (SNRI), mirtazapine, or bupropion is optimal [LoE: I]
• 'In general, the use of nonselective monoamine oxidase inhibitors (MAOIs) (e.g., phenelzine, tranylcypromine, isocarboxazid) should be restricted to patients who do not respond to other treatments [LoE: I]…'</td></tr>
</table>

	• In patients who prefer complementary and alternative therapies, S-adenosyl methionine (SAMe) [LoE: III] or St. John's wort [LoE: III] might be considered, although evidence for their efficacy is modest at best, and careful attention to drug-drug interactions is needed with St. John's wort [LoE: I] • During the acute phase of treatment, patients should be carefully and systematically monitored on a regular basis to assess their response to pharmacotherapy, identify the emergence of side effects (e.g., gastrointestinal symptoms, sedation, insomnia, activation, changes in weight, and cardiovascular, neurological, anticholinergic, or sexual side effects), and assess patient safety [LoE: I] • If antidepressant side effects do occur, an initial strategy is to lower the dose of the antidepressant or to change to an antidepressant that is not associated with that side effect [LoE: I] <u>Other somatic therapies</u> • ECT is recommended as a treatment of choice for patients with severe major depressive disorder that is not responsive to psychotherapeutic and/or pharmacological interventions, particularly in those who have significant functional impairment or have not responded to numerous medication trials [LoE: I] • ECT is also recommended for individuals with major depressive disorder who have associated psychotic or catatonic features [LoE: I], for those with an urgent need for response (e.g., patients who are suicidal or nutritionally compromised due to refusal of food or fluids) [LoE: I], and for those who prefer ECT or have had a previous positive response to ECT [LoE: II] • Bright light therapy might be used to treat seasonal affective disorder as well as nonseasonal depression [LoE: III] <u>Psychotherapy</u> • Use of a depression-focused psychotherapy alone is recommended as an initial treatment choice for patients with mild to moderate major depressive disorder [LoE: I], with clinical evidence supporting the use of cognitive-behavioral therapy (CBT) [LoE: I], interpersonal psychotherapy [LoE: I], psychodynamic therapy [LoE: II], and problem-solving therapy [LoE: III] in individual [LoE: I] and in group [LoE: III] formats. • Considerations in the choice of a specific type of psychotherapy include the goals of treatment (in addition to resolving major depressive symptoms), prior positive response to a specific type of psychotherapy, patient preference, and the availability of clinicians skilled in the specific psychotherapeutic approach [LoE: II] • As with patients who are receiving pharmacotherapy, patients receiving psychotherapy should be carefully and systematically monitored on a regular basis to assess their response to treatment and assess patient safety [LoE: I] <u>Psychotherapy plus antidepressant medication</u> • The combination of psychotherapy and antidepressant medication may be used as an initial treatment for patients with moderate to severe major depressive disorder [LoE: I]. • In addition, combining psychotherapy and medication may be a useful initial treatment even in milder cases for patients with psychosocial or interpersonal problems, intrapsychic conflict, or co-occurring Axis II disorder [LoE: II]. • In general, when choosing an antidepressant or psychotherapeutic approach for combination treatment, the same issues should be considered as when selecting a medication or psychotherapy for use alone [LoE: I]. **Strategies to address nonresponse:** • For individuals who have not responded fully to treatment, the acute phase of treatment should not be concluded prematurely [LoE: I], as an incomplete

	response to treatment is often associated with poor functional outcomes. • If at least a moderate improvement in symptoms is not observed within 4–8 weeks of treatment initiation, the diagnosis should be reappraised, side effects assessed, complicating co-occurring conditions and psychosocial factors reviewed, and the treatment plan adjusted [LoE: I]. • For patients in psychotherapy, additional factors to be assessed include the frequency of sessions and whether the specific approach to psychotherapy is adequately addressing the patient's needs [LoE: I]. • If medications are prescribed, the psychiatrist should determine whether pharmacokinetic [LoE: I] or pharmacodynamics [LoE: III] factors suggest a need to adjust medication doses. With some TCAs, a drug blood level can help determine if additional dose adjustments are required [LoE I]. • After an additional 4–8 weeks of treatment, if the patient continues to show minimal or no improvement in symptoms, the psychiatrist should conduct another thorough review of possible contributory factors and make additional changes in the treatment plan [LoE: I]. Consultation should also be considered [LoE: II]. • A number of strategies are available when a change in the treatment plan seems necessary. For patients treated with an antidepressant, optimizing the medication dose is a reasonable first step if the side effect burden is tolerable and the upper limit of a medication dose has not been reached [LoE: II]. • Particularly for those who have shown minimal improvement or experienced significant medication side effects, other options include augmenting the antidepressant with a depression-focused psychotherapy [LoE: I] or with other agents [LoE: II] or changing to another non-MAOI antidepressant [LoE: I]. • Patients may be changed to an antidepressant from the same pharmacological class (e.g., from one SSRI to another SSRI) or to one from a different class (e.g., from an SSRI to a tricyclic antidepressant [TCA]) [LoE: II]. • For patients who have not responded to trials of SSRIs, a trial of an SNRI may be helpful [LoE: II]. Augmentation of antidepressant medications can utilize another non-MAOI antidepressant [LoE: II], generally from a different pharmacological class, or a non-antidepressant medication such as lithium [LoE: II], thyroid hormone [LoE: II], or a second-generation antipsychotic [LoE: II]. • Additional strategies with less evidence for efficacy include augmentation using an anticonvulsant [LoE: III], omega-3 fatty acids [LoE: III], folate [LoE: III], or a psychostimulant medication [LoE: III], including modafinil [LoE: III]. • If anxiety or insomnia are prominent features, consideration can be given to anxiolytic and sedative-hypnotic medications [LoE: III], including buspirone, benzodiazepines, and selective □-aminobutyric acid (GABA) agonist hypnotics (e.g., zolpidem, eszopiclone). • For patients whose symptoms have not responded adequately to medication, ECT remains the most effective form of therapy and should be considered [LoE: I]. • In patients capable of adhering to dietary and medication restrictions, an additional option is changing to a nonselective MAOI [LoE: II] after allowing sufficient time between medications to avoid deleterious interactions [LoE: I]. • Transdermal selegiline, a relatively selective MAO B inhibitor with fewer dietary and medication restrictions, or transcranial magnetic stimulation could also be considered [LoE: II]. • Vagus nerve stimulation (VNS) may be an additional option for individuals who have not responded to at least four adequate trials of antidepressant treatment, including ECT [LoE: III]. • For patients treated with psychotherapy, consideration should be given to increasing the intensity of treatment or changing the type of therapy [LoE: II]. • If psychotherapy is used alone, the possible need for medications in addition

	to or in lieu of psychotherapy should be assessed [LoE: I]. • Patients who have a history of poor treatment adherence or incomplete response to adequate trials of single treatment modalities may benefit from combined treatment with medication and a depression-focused psychotherapy [LoE: II].
Malhi et al. 2009: Clinical practice recommendations for depression	**'PACE': treatment options for depression** *Note: The acronym ``PACE'' denotes the recommended treatment options for depression in the order they should be considered. However, treatment choice depends upon individual factors and treatment availability.* **P: Psychological treatment (level I)** • Consider psychological interventions especially if indicated by clinical features (e.g. presence of psychosocial issues, grief, loss and interpersonal problems). • Psychological therapies have efficacy comparable with antidepressant medications in the treatment of depression, where depressive features are not severe (HAM-D < 25), and there are no psychotic features. • There is a substantive evidence base for CBT (level I), IPT (level I) and BAS (level I) (e.g. activity scheduling). **A: Antidepressant treatment (level I)** **RATE:** When selecting an antidepressant consider: ***R**isk, **A**dherence, **T**olerability and **E**fficacy.* ***R**: Risk*: TCAs and MAOIs are potentially lethal in overdose and can produce toxicity through interactions with other medications. SSRIs and other newer antidepressants can rarely cause serotonin syndrome and the risk of this should be considered. ***A**: Adherence:* Adherence to the prescribed dose of antidepressant is essential. Dosing of medications should be as simple and convenient as possible in order to enhance adherence. Psychological engagement improves medication adherence. ***T**: Tolerability:* The side-effect profile of medications is a key determinant of antidepressant choice. Tolerability impacts upon adherence and outcome and should be routinely assessed. Common treatment side-effects should be discussed at the outset of treatment. ***E**: Efficacy:* Antidepressants may take up to 14 days to take effect but usually some improvement is discernible much earlier. Antidepressants are not addictive but abrupt cessation can precipitate withdrawal symptoms (especially with paroxetine, venlafaxine and TCAs). Therefore, when withdrawn, antidepressants should be tapered gradually. • SSRI: SSRIs are generally better tolerated than other classes of antidepressants and are suitable first-line. Sexual dysfunction and gastrointestinal symptoms are common. Many SSRIs (especially fluoxetine and paroxetine) cause significant CYP450 inhibition and care is needed when co-prescribed with other medications. • NARI (reboxetine): Reboxetine is suitable first-line. Common side-effects include hypersomnia, fatigue and nausea. • NaSSA (mirtazapine): Mirtazapine, a suitable first-line option, is associated with weight gain and drowsiness. • SNRI (venlafaxine, desvenlafaxine and duloxetine): SNRIs appear to be more effective than SSRIs in treating severe depressive symptoms (HAM-D≥) and melancholia. In some cases, adverse effects may limit SNRIs to second-line treatment. However, if depression is severe (i.e. HAM-D >25), then SNRIs are a suitable first-line option. Sexual dysfunction and gastrointestinal symptoms are common with venlafaxine. • TCA: In comparison with SSRIs, TCAs have a greater side-effect burden (anticholinergic and CNS) and toxicity in overdose and therefore are considered second-line. However, TCAs (especially those that have both noradrenergic and serotonergic activity such as amitriptyline and clomipramine) may be more effective when compared with other

	antidepressants in treating severe depressive symptoms (HAM-D ≥25), in particular patients with melancholia and those hospitalized because of severe depression. • MAOIs: Efficacious antidepressants but not recommended first-line because of risk of hypertensive crisis if necessary dietary and drug interaction restrictions are not adhered to. **C: Combining antidepressants and psychological therapies (level I)** Consider psychological and antidepressant combination treatment if response to single modality has been suboptimal or failed, or if indicated by clinical features. • Combination therapies are more effective and reduce time to remission than either psychological or antidepressant treatment alone, especially in depression of moderate or greater severity (HAM-D ≥18) and chronic depression (level I). **E: ECT (level I)** ECT is administered under general anaesthesia, either bilaterally or unilaterally, usually in an in-patient setting. The most common side-effect is cognitive impairment that is usually transient; however, there is also evidence that suggests some risk of longer term memory impairment. • ECT is a safe and effective treatment (80–82), that is also effective when pharmacotherapy has failed (82, 83), although the risk of relapse remains. • Consider ECT if there is a high risk of suicide, greater severity, significant psychotic symptoms or if there has been a previous response to ECT treatment. **Continuing treatment** • Evidence of an antidepressant effect is most likely to occur within the first 2 weeks of treatment. If no response occurs within this time period or if the patient fails to respond adequately within a reasonable time frame (up to 6 weeks), a treatment change is indicated. If remission is not achieved by 3 months, seek consultation or a second opinion and continue active treatment *(level V).* • Expert consensus recommends continuation of antidepressant treatment for at least 1 year following the onset of symptoms for an initial episode and 3 years for recurrent episodes *(level V).* If an initial episode included psychotic features, then continue treatment for at least 3 years. • If there are residual negative cognitions or relationship issues, consider psychological interventions such as CBT/IPT.

IQWIG Berichte/G-BA Beschlüsse

IQWIG, 2009: Leitliniensynopse zum Thema "Depression"	**Population**: Die Zielpopulation der eingeschlossenen Leitlinien sind Männer und Frauen im Alter von 18 bis 65 Jahren mit unipolarer majorer Depression („Major Depression“, ICD-10: F32, F33, F34). **Siehe zusammenfassende Tabellen zur Therapie in Anlage 1!**
IQWIG, 2009: Selektive Serotonin- und Noradrenalin-Wiederaufnahmehemmer (SNRI) bei Patienten mit Depressionen *Hinweis*: Zu diesem Abschlussbericht liegt akutell eine neue Version (Version 1.1, 2010) vor. Keine der vorgenommenen Änderungen im Vergleich zum Abschlussbericht der Version 1.0 führte zu einer Änderung des Fazits des Berichts.	**Ziele der Untersuchung:** • Die Nutzenbewertung der selektiven Serotonin- und Noradrenalin-Wiederaufnahmehemmer (SNRI) Venlafaxin und Duloxetin bei der Behandlung der akuten Phase der Depression, bei der Erhaltungstherapie (Rückfallprävention) und bei der Rezidivprophylaxe im Vergleich zu einer Placebogabe und • Die Nutzenbewertung der selektiven Serotonin- und Noradrenalin-Wiederaufnahmehemmer (SNRI) Venlafaxin und Duloxetin bei der Behandlung der akuten Phase der Depression, bei der Erhaltungstherapie (Rückfallprävention) und bei der Rezidivprophylaxe im Vergleich untereinander und zu anderen Antidepressiva jeweils bei Patienten mit Depressionen hinsichtlich patientenrelevanter Therapieziele. **Population:** Für die Nutzenbewertung wurden Studien mit Patienten mit einer leichten, mittelschweren oder schweren Depression berücksichtigt. Die Diagnosesicherung sollte dabei anhand allgemein akzeptierter Kriterien (d. h. nach ICD-, DSM- oder RDC-Kriterien) erfolgt sein. Es wurden auch Studien mit Patienten mit somatischer bzw. psychiatrischer Komorbidität berücksichtigt. Depression musste hierbei die psychiatrische Primärdiagnose sein. Die Antidepressiva mussten in erster Linie zur Depressionsbehandlung (und nicht z. B. zur Angstbehandlung) verwendet worden sein. **Endpunkte**: Remission, Änderung der depressiven Symptomatik (Ansprechen und mittlere Änderung der depressiven Symptomatik gemessen auf einer Skala), Rückfall und Rezidiv, Einzel- und Begleitsymptome der Depression, gesundheitsbezogene Lebensqualität, soziales Funktionsniveau, Mortalität, Suizidalität, die Gesamtraten unerwünschter Ereignisse und schwerwiegender unerwünschter Ereignisse, Therapieabbrüche wegen unerwünschter Ereignisse, sexuelle Dysfunktion und Bluthochdruck **Ergebnis /Fazit (*fokussierte Ergebniswiedergabe auf direkten Vergleich*):** Direktvergleich : • Beleg für einen größeren Schaden von Duloxetin bzw. für einen geringeren Schaden von Venlafaxin bezüglich der Therapieabbrüche wegen unerwünschter Ereignisse Venlafaxin • Beleg für einen Zusatznutzen im Vergleich zu der Wirkstoffklasse der SSRI (auf Ebene der Einzelwirkstoffe für Fluoxetin) für die Änderung der depressiven Symptomatik (Ansprechen) in der Kurzzeit-Akuttherapie • Beleg für einen Zusatznutzen im Vergleich zu Bupropion für die Remission und die Änderung der depressiven Symptomatik (Ansprechen) in der Kurzzeit-Akuttherapie • Hinweis darauf, dass für die Änderung der depressiven Symptomatik (Ansprechen) der Zusatznutzen von Venlafaxin gegenüber SSRI eher für Patienten mit höherem Schweregrad der Depression gilt als für Patienten mit niedrigerem Schweregrad • Beleg für einen größeren Schaden im Vergleich zu SSRI (auf Ebene der Einzelwirkstoffe für Fluoxetin) für die Gesamtrate unerwünschter

	Ereignisse und Therapieabbrüche wegen unerwünschter Ereignisse in der Kurzzeit-Akuttherapie • Beleg für einen größeren Schaden im Vergleich zu Agomelatin für die Therapieabbrüche wegen unerwünschter Ereignisse in der Kurzzeit-Akuttherapie • Beleg für einen geringeren Schaden im Vergleich zu TZA und Amitriptylin sowie Clomipramin für die Gesamtrate unerwünschter Ereignisse in der Kurzzeit-Akuttherapie • Hinweis auf einen geringeren Schaden im Vergleich zu Maprotilin für die Therapieabbrüche wegen unerwünschter Ereignisse in der Kurzzeit-Akuttherapie • Hinweis auf einen geringeren Schaden im Vergleich zu Trazodon für die Gesamtrate unerwünschter Ereignisse in der Kurzzeit-Akuttherapie • Alle weiteren verfügbaren Kombinationen von Endpunkten, Therapievergleichen und therapeutischen Zielen lieferten keine Belege oder Hinweise für einen Nutzen bzw. Zusatznutzen oder für einen Schaden bzw. größeren oder geringeren Schaden von Duloxetin oder Venlafaxin im Vergleich zu Placebo oder aktiven Komparatoren. • Für die Endpunkte Mortalität und Suizidalität ist aufgrund der eingeschränkten Datenlage für beide Substanzen keine abschließende Aussage möglich. Für die Bewertung des Einflusses auf Komplikationen von ggf. die Depression begleitenden Erkrankungen lagen keine Daten vor.
G-BA, 2011: Zusammenfassende Dokumentation über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage IX – Festbetragsgruppenbildung und Anlage X – Aktualisierung von Vergleichsgrößen Selektive Serotonin-Wiederaufnahmehemmer, Gruppe 1, in Stufe 2 nach § 35 Absatz 1 SGB V.	**Fazit:** Der Unterausschuss „Arzneimittel“ hat die in den Stellungnahmen angeführten Argumente gründlich geprüft. Es liegen keine Belege vor, die eine signifikante und klinisch relevante therapeutische Verbesserung von Escitalopram vs. Citalopram zeigen. Die Voraussetzung nach § 35 Abs. 1 S. 3 HS. 2 SGB V liegt somit für den unter Patentschutz stehenden Wirkstoff Escitalopram nicht vor. Die vorgeschlagene Neubildung der Festbetragsgruppe „Selektive Serotonin-Wiederaufnahmehemmer, Gruppe 1“ in Stufe 2 ist sachgerecht und entspricht den Vorgaben des § 35 Abs. 1 SGB V.
IQWIG, 2009: Bupropion, Mirtazapin und Reboxetin bei der Behandlung der Depression *Hinweis*: Zu diesem Abschlussbericht liegt akutell eine neue Version (Version 1.1, 2011) vor. Keine der vorgenommenen Änderungen im Vergleich zum Abschlussbericht der Version 1.0 führte zu einer Änderung des Fazits des Berichts.	**Ziel:** Die Nutzenbewertung einer Behandlung mit Bupropion, Mirtazapin oder Reboxetin bei der Behandlung der akuten Phase der Depression, bei der Erhaltungstherapie (Rückfallprävention) und bei der Rezidivprophylaxe − im Vergleich zu einer Behandlung mit Placebo, − im Vergleich untereinander oder − im Vergleich zu einer Behandlung mit anderen Antidepressiva, jeweils bei erwachsenen Patienten mit Depression hinsichtlich patientenrelevanter Therapieziele. **Ergebnisse (*fokussierte Ergebniswiedergabe zur Aktutherapie*):** Mirtazapin in der Akuttherapie: • Es gibt keine Belege für einen Zusatznutzen von Mirtazapin im Vergleich zu anderen Antidepressiva für die Zielgrößen Remission, Response und mittlere Änderung der depressiven Symptomatik in der Kurzzeit- oder Langzeitakuttherapie. Ebenfalls gibt es keinen Beleg für einen Zusatznutzen von Mirtazapin bezüglich des sozialen Funktionsniveaus oder der gesundheitsbezogenen Lebensqualität. • Im Vergleich zu anderen Antidepressiva sind ein größerer Schaden von Mirtazapin im Vergleich zu Fluoxetin und ein geringerer Schaden von Mirtazapin im Vergleich zu Paroxetin für Therapieabbrüche wegen unerwünschter Ereignisse in der Kurzzeitakuttherapie belegt. Für die Therapieabbrüche wegen unerwünschter Ereignisse gibt es darüber hinaus einen Hinweis auf einen größeren Schaden von Mirtazapin im Vergleich zu Sertralin für depressive Patienten ohne weitere

	Einschränkung und für SSRI-resistente depressive Patienten. • Bezüglich schwerwiegender unerwünschter Ereignisse gibt es einen Hinweis auf einen größeren Schaden von Mirtazapin im Vergleich zu Venlafaxin XR in der Kurzzeitakuttherapie. Die weiteren aktiven Vergleiche zeigten bezüglich unerwünschter Ereignisse keine Belege für einen größeren oder geringeren Schaden von Mirtazapin. Ein Beleg für einen größeren oder geringeren Schaden von Mirtazapin im Vergleich zu anderen Antidepressiva bezüglich der sexuellen Dysfunktion liegt nicht vor. <u>Bupropion XL in der Kurzzeitakuttherapie</u> • Im Vergleich zu Venlafaxin XR ist in der Kurzzeitakuttherapie ein geringerer Nutzen von Bupropion XL für die Remission und die Response belegt. Der Zusatznutzen oder geringere Nutzen bezüglich der mittleren Änderung der depressiven Symptomatik, gemessen auf der MADRS, ist nicht belegt. • Der Nutzen von Bupropion XL im Vergleich zu Placebo bezüglich des sozialen Funktionsniveaus, der gesundheitsbezogenen Lebensqualität, der Angstsymptomatik sowie der Motivation und Energie der Patienten ist in der Kurzzeitakuttherapie nicht belegt. Ein Vergleich von Bupropion XL und Venlafaxin XR ergibt für diese genannten Zielgrößen keinen Beleg für einen Zusatznutzen von Bupropion XL. • Unter Beachtung der limitierten Aussagekraft der Daten ergaben sich für die Suizidalität, Suizide oder Mortalität keine Belege für einen Schaden von Bupropion XL im Vergleich zu Placebo oder für einen größeren oder geringeren Schaden im Vergleich zu Venlafaxin XR in der Kurzzeitakuttherapie. • Es gibt in der Kurzzeitakuttherapie keine Belege für einen Schaden von Bupropion XL im Vergleich zu Placebo oder für einen größeren oder geringeren Schaden im Vergleich zu Venlafaxin XR für unerwünschte Ereignisse und Therapieabbrüche wegen unerwünschter Ereignisse oder sexuelle Dysfunktion. Für die schwerwiegenden unerwünschten Ereignisse zeigte sich ein Beleg für einen geringeren Schaden von Bupropion XL verglichen mit Placebo (hervorgerufen durch Verschlechterungen der Grunderkrankung in der Placebogruppe). Im Vergleich zu Venlafaxin XR liegt kein Beleg für einen größeren oder geringeren Schaden von Bupropion XL bezüglich schwerwiegender unerwünschter Ereignisse vor.
G-BA, 2010: Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über die Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage III – Übersicht der Verordnungseinschränkungen und –ausschlüsse Reboxetin	**Fazit:** • Dem Gemeinsamen Bundesausschuss wurde als Empfehlung die Nutzen-bewertung von Bupropion, Mirtazapin und Reboxetin bei der Behandlung der Depression übermittelt (Version 1.0 vom 09.11.2009 / Auftrag A05-20C). • Der Unterausschuss „Arzneimittel“ ist nach Würdigung des Abschlussberichts des IQWiG und der Beratungen der Arbeitsgruppe „Nutzenbewertung“ zu dem Ergebnis gekommen, dass die tatbestandlichen Voraussetzungen für einen Ver-ordnungsausschluss von Reboxetin gemäß § 92 Abs. 1 Satz 1, letzter Halbsatz SGB V erfüllt sind.
G-BA, 2209: Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über die Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage I (OTC-Übersicht)	**Fazit**: Entsprechend der geänderten Verordnung über die Verschreibungspflicht von Arzneimitteln unterliegt Johanniskraut (Hypericum perforatum) zur Behandlung mittelschwerer Depressionen nun mehr der Verschreibungs-pflicht, so dass die entsprechende Regelung in Nr. 22 der Anlage I entfällt.
G-BA, 2011: Zusammenfassende Dokumentation über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage IX	**Fazit:** Der Unterausschuss „Arzneimittel“ kommt zu dem Schluss, dass die vorgeschlagene Neubildung der Festbetragsgruppe „Venlafaxin, Gruppe 1“ in Stufe 1 sachgerecht ist und den Vorgaben des § 35 Abs. 1 SGB V entspricht.

– Festbetragsgruppenbildung Venlafaxin, Gruppe 1, in Stufe 1 nach § 35 Absatz 1 SGB V	
G-BA, 2011: Zusammenfassende Dokumentation über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage IX – Festbetragsgruppenbildung Antipsychotika, andere, Gruppe 1, in Stufe 2 nach § 35 Absatz 1 SGB V	**Fazit:** Der Unterausschuss „Arzneimittel“ hat die in der Stellungnahme angeführten Argumente gründlich geprüft. Er kommt zu dem Schluss, dass die vorgelegten Argumente eine pharmakologisch-therapeutische Nicht-Vergleichbarkeit, auch wegen geringerer Nebenwirkungen, nicht rechtfertigen. Es liegen keine Belege für die Therapie bedeutsame überlegene Wirksamkeit von einem Wirkstoff gegenüber dem anderen vor, auch nicht in Bezug auf die neu einzugruppierende Darreichungsform. Die vorgeschlagene Aktualisierung der Festbetragsgruppe „Antipsychotika, andere, Gruppe 1“ in Stufe 2 ist sachgerecht ist und entspricht den Vorgaben des § 35 Abs. 1 SGB V.

Cochrane Reviews

Cipriani et al. 2012: Duloxetine versus other anti-depressive agents for depression	Systematische Literaturrecherche bis 2012. **Population:** Erwachsene Patienten (> 18 Jahre) mit majorer Depression **Vergleiche:** • Duloxetin vs. konventionelle Behandlung (inkl. trizyklische Antidepressiva; heterozyklische Mittel; SSRIs; SNRIs; MAOIs oder neuere Antidepressiva; andere konventionelle Psychopharmaka) • Duloxetin vs. nicht-konventionelle Antidepressiva (z.B. pflanzliche Produkte, andere nicht-konventionelle Antidepressiva) **Endpunkte:** • Primärer Endpunkt**:** Ansprechen in der akuten Behandlungsphase (mind. 50% auf Hamilton Rating Scale for major depression Skala [HAM-D], Montgomery Åsberg Depression Rating Scale [MADRS] oder einer anderen Skala) • Sekundäre Endpunkte: Ansprechen in weiteren Behandlungsphasen, Remission (alle Phasen), Veränderung auf der Depressionsskala am Ende der Studie (durchschn. Gruppenunterschied), Lebensqualität, soziales Funktionieren, Kosten, Verträglichkeit, Dropout (allgemein, aufgrund von Nebenwirkungen, aufgrund von Unwirksamkeit), Nebenwirkungen (Anzahl Patienten die mind. 1 Nebenwirkungen erfuhren), spezifische Nebenwirkungen ('sleepiness/drowsiness,insomnia, dry mouth, constipation, problems urinating, hypotension, agitation/anxiety, suicide wishes/gestures/attempts, completed suicide, vomiting/nausea, diarrhoea') **Ergebnisse (basierend auf 16 Studien mit insgesamt 5735 Patienten):** Duloxetin vs. • SSRI (Paroxetin, Escitalopram und Fluoxetin) basierend auf 11 Studien mit insgesamt 3304 Patienten • neuere Antidepressiva (Venlafaxin, Desvenlafaxin) basierend auf 4 Studien mit insgesamt 1978 Patienten • Neuroleptika (Quetiapin) (basierend auf einer Studie mit insgesamt 453 Patienten) Wirksamkeit: • Es zeigten sich keine statistisch signifikanten Unterschiede zwischen Duloxetin und anderen Antidepressiva hinsichtlich der Wirksamkeitsendpunkte. Sicherheit: • Wenn gegen Escitalopram oder Venlafaxin verglichen wurde, zeigte sich eine höhere Dropout Rate unter Duloxetin aufgrund jeglicher Ursachen (OR: 1.62; 95% KI: 1.01 - 2.62 und OR: 1.56; 95% KI: 1.14 - 2.15). • Es zeigte sich unter Duloxetin ein nachteiliger Effekt hinsichtlich der unerwünschten Ereignisse wenn auch nicht stat. signifikant, wenn verglichen wurde gegen Paroxetin. *Hinweis*: Es wurden keine Studien identifiziert, die Duloxetin mit trizyklischen Antidepressiva verglichen haben. Fazit der Autoren: *'Duloxetine did not seem to provide a significant advantage in efficacy over other antidepressive agents for the acute-phase treatment of major depression. No differences in terms of efficacy were found, even though*

	duloxetine was worse than some SSRIs (most of all, escitalopram) and newer antidepressants (like venlafaxine) in terms of acceptability and tolerability. Unfortunately, we only found evidence comparing duloxetine with a handful of other active antidepressive agents and only a few trials per comparison were found (in some cases we retrieved just one trial). This limited the power of the review to detect moderate, but clinically meaningful differences between the drugs. As many statistical tests have been used in the review, the findings from this review are better thought of as hypothesis forming rather than hypothesis testing and it would be very comforting to see the conclusions replicated in future trials. Most of included studies were sponsored by the drug industry manufacturing duloxetine. As for all other new investigational compounds, the potential for overestimation of treatment effect due to sponsorship bias should be borne in mind. In the present review no trials reported economic outcomes. Given that several SSRIs and the great majority of antidepressants are now available as generic formulation (only escitalopram, desvenlafaxine and duloxetine are still on patent), more comprehensive economic estimates of antidepressant treatment effect should be considered to better inform healthcare policy.' **Anmerkungen der Autoren und FBMed:** • Teils fehlende Qualitätsangaben in den Studien (z.B. Informationen zum Allocation Concealment und Verblindung) • Bericht zu den Nebenwirkungen war zwischen den Studien unterschiedlich • Die meisten Studien wurden von der Industrie gesponsert.
Cipriani et al. 2012: Citalopram versus other anti-depressive agents for depression	Systematische Literaturrecherche bis 2012. **Population:** Erwachsene Patienten (>18 Jahre) mit Depression **Vergleiche:** Citalopram vs. konventionelle Behandlung (inkl. trizyklische Antidepressiva; heterozyklische Mittel; SSRIs; SNRIs; MAOIs oder neuere Antidepressiva; andere konventionelle Psychopharmaka, nicht-konventionelle Antidepressiva [wie: pflanzliche Produkte, andere nicht-konventionelle Antidepressiva]) **Endpunkte:** • <u>Primärer Endpunkt</u>: Ansprechen in der akuten Behandlungsphase (mind. 50% auf der HAM-D, der MADRS oder einer anderen Skala) • <u>Sekundäre Endpunkte:</u> Ansprechen in weiteren Behandlungsphasen, Remission (alle Phasen), Veränderung auf der Depressionsskala am Ende der Studie (durchschn. Gruppenunterschied), Lebensqualität, soziales Funktionieren, Kosten, Verträglichkeit, Dropout (allgemein, aufgrund von Nebenwirkungen, aufgrund von Unwirksamkeit), Nebenwirkungen (Anzahl Patienten die mind. 1 Nebenwirkungen erfuhren), spezifische Nebenwirkungen ('sleepiness/drowsiness,insomnia, dry mouth, constipation, problems urinating, hypotension, agitation/anxiety, suicide wishes/gestures/attempts, completed suicide, vomiting/nausea, diarrhoea') **Ergebnisse (basierend auf 37 Studien):** <u>Wirksamkeit:</u> • Es zeigte sich eine stat. signifikante Unterlegenheit von Citalopram gegenüber Escitalopram hinsichtlich des Erreichens eines akuten Ansprechens (OR: 1.47, 95% KI: 1.08- 2.02), jedoch eine stat. signifikante Überlegenheit gegenüber Paroxetin (OR: 0.65, 95% KI: 0.44 -0.96) und Reboxetin (OR: 0.63, 95% KI: 0.43-0.91). <u>Sicherheit:</u> • Statistisch signifikant weniger Patienten brachen die Studie unter Citalopram aufgrund von Nebenwirkungen ab, wenn verglichen wurde

	gegenüber trizyklische Antidepressiva (OR: 0.54, 95% KI: 0.38-0.78). • Statistisch signifikant weniger Patienten berichteten mind. 1 Nebenwirkung erfahren zu haben, wenn verglichen wurde gegen Reboxetin oder Venlafaxin (OR: 0.64, 95% KI 0.42- 0.97 und OR: 0.46, 95% KI 0.24-0.88). Fazit der Autoren: *'Some statistically significant differences between citalopram and other antidepressants for the acute phase treatment of major depression were found in terms of efficacy, tolerability and acceptability. Citalopram was more efficacious than paroxetine and reboxetine and more acceptable than tricyclics, reboxetine and venlafaxine, however, it seemed to be less efficacious than escitalopram. As with most systematic reviews in psychopharmacology, the potential for overestimation of treatment effect due to sponsorship bias and publication bias should be borne in mind when interpreting review findings. Economic analyses were not reported in the included studies, however, cost effectiveness information is needed in the field of antidepressant trials.'* **Anmerkungen der Autoren und FBMed:** • Teils fehlende Qualitätsangaben in den Studien (z.B. Informationen zum Allocation Concealment und der Randomisierung)
Cipriani et al. 2010: Sertraline versus other antidepressive agents for depression	Systematische Literaturrecherche bis 2008. **Population:** Erwachsene Patienten (> 18 Jahre) mit majorer Depression **Vergleiche:** Sertralin vs. andere Antidepressiva (inkl. konventionelle trizyklische Antidepressiva, heterozyklische Mittel (z.B. Maprotilin), SSRIs (Fluoxetin, Fluvoxamin, Citalopram, Paroxetin, Escitalopram), neuere Antidepressiva (SNRIs wie Venlafaxin, Duloxetin, Milnacipran); MAOIs oder neuere Arzneimittel wie Mirtazapin, Bupropion, Reboxetin; und nicht-konventionelle Antidepressiva (z.B. pflanzliche Produkte) **Endpunkte:** Therapieansprechen (primärer Endpunkt), Remission, Veränderung auf der Depressionsskala am Ende der Studie, Lebensqualität, soziales Funktionieren, Kosten, Verträglichkeit, Dropout (allgemein, aufgrund von Nebenwirkungen, aufgrund von Unwirksamkeit), Nebenwirkungen allgemein, spezifische Nebenwirkungen **Ergebnisse (basierend auf 59 Studien von meist schlechter Qualität; fokussiert auf die akute Behandlungsphase):** **Wirksamkeit:** Sertralin vs. trizyklische Antidepressiva: • Stat. signifikanter Vorteil hinsichtlich der Remission unter Sertralin gegenüber Imipramin in der akuten Behandlungsphase (OR: 0.67, 95% KI: 0.45 - 0.99, p = 0.05; basierend auf 3 Studien mit N= 482 Patienten). • Stat. signifikanter Nachteil unter Sertralin gegenüber Amitriptylin hinsichtlich einer Veränderung auf der Depressionsskala am Ende der Studie in der akuten Behandlungsphase (SMD: 0.18, 95% KI 0.04 - 0.32, p = 0.009; basierend auf 7 Studien mit N=1172 Patienten). • Zu den anderen Wirksamkeitsendpunkten wurden keine Unterschiede identifiziert oder es lagen keine Daten vor. Sertralin vs. heterozyklische Mittel: • Kein Unterschied oder keine Daten vorhanden. Sertralin vs. andere SRRIs: • Stat. signifikanter Vorteil unter Sertralin gegenüber Fluoxetin hinsichtlich dem Therapieansprechen (OR: 0.73, 95% KI: 0.59 - 0.92, p = 0.007;

	basierend auf 8 Studien mit N=1352). • Zu den anderen Wirksamkeitsendpunkten wurden keine Unterschiede identifiziert oder es lagen keine Daten vor. <u>Sertralin vs. neuere Antidepressiva:</u> • Keine Unterschiede zwischen den Substanzen oder keine Daten vorhanden. **Sicherheit:** **Studienabbruchrate:** • Stat. signifikant weniger Patienten brachen die Studie aufgrund jeglicher Ursache unter Sertralin ab, wenn verglichen wurde gegenüber Imipramin (TCA) (OR: 0.62, 95% KI: 0.40 - 0.96, p = 0.03; basierend auf 5 Studien mit N= 641 Patienten), Mirtazapin (neueres Antidepressivum) (OR: 0.68, 95% KI: 0.47 - 0.99, p = 0.05; basierend auf 2 Studien mit N=596 Patienten) und Bupropion (neueres Antidepressivum) (OR: 1.42, 95%KI: 1.02- 1.99, p = 0.04; basierend auf 3 Studien mit N=727 Patienten). • Stat. signifikant weniger Patienten brachen die Studie unter Sertralin aufgrund von Nebenwirkungen ab, wenn gegenüber Paroxetin (OR: 0.28, 95%KI: 0.08 - 0.96, p = 0.04; basierend auf 3 Studien mit N= 311 Patienten), Mirtazaptin (neueres Antidepressivum) (OR: 0.35, 95%KI: 0.17 - 0.74, p = 0.06; basierend auf 2 Studien mit N=596 Patienten) und Venlafaxin (neueres Antidepressivum) (OR: 0.33, 95% KI: 0.17 - 0.64, p = 0.001; basierend auf 5 Studien mit N=611 Patienten) getestet wurde. **Allgemeine Nebenwirkungen:** • Stat. signifikante Vorteile unter Sertralin gegenüber Amitriptylin (TCA) (OR 0.59, 95% KI: 0.39 - 0.89, p = 0.01; basierend auf 5 Studien mit N=999 Patienten) oder Imipramin (OR: 0.17, 95% KI: 0.09 - 0.32, P<0.00001; basierend auf 2 Studien mit N=209 Patienten). • Stat. Nachteile wenn verglichen wurde gegen Escitalopram (OR: 1.76, 95%KI 1.06 - 2.94, p=0.03; basierend auf 2 Studien mit N= 489 Patienten). • Zu den anderen Substanzen lagen keine Daten vor bzw. wurden keine Unterschiede identifiziert. **Individuelle Nebenwirkungen:** • Allgemein erfuhren mehr Patienten unter einer Therapie mit Sertralin gastrointestinale Ereignisse, insbesondere Durchfälle. • Hinsichtlich der anderen Nebenwirkungen lagen heterogene Ergebnisse vor. <u>Fazit der Autoren:</u> *'This systematic review and meta-analysis highlighted a trend in favour of sertraline over other antidepressive agents both in terms of efficacy and acceptability, using 95% confidence intervals and a conservative approach, with a random effects analysis. However, the included studies did not report on all the outcomes that were pre-specified in the protocol of this review. Outcomes of clear relevance to patients and clinicians were not reported in any of the included studies.'* **Anmerkungen der Autoren und FBMed:** • Studien allgemein von schlechter Qualität
Cipriani et al. 2009 Escitalopram versus other antidepressive agents for depression	Systematische Literaturrecherche bis Juli 2008. **Population:** Erwachsene Patienten (> 18 Jahre) mit majorer Depression **Vergleiche:** • Escitalopram vs. SSRI (14 Studien) • Escitalopram vs. neueres Antidepressivum (Venlafaxin, Bupropion und

	Duloxetin) (8 Studien) **Endpunkte:** <u>Primärer Endpunkt:</u> Therapieansprechen (mind. 50% entsprechend der HAM-D oder MADRS oder einer anderen Depressionsskala <u>Sekundärer Endpunkt:</u> Remission, Veränderung auf der Depressionsskala (Baseline bis Ende der Studie), soziale Anpassung und soziales Funktionieren, Kosten, Dropout (allgemein, aufgrund von Nebenwirkungen, aufgrund von Unwirksamkeit), Verträglichkeit (Anzahl Patienten die mind. 1 Nebenwirkungen erlitten), spezifische Nebenwirkungen (z.B. Agitation / Angst, Verstopfung, Durchfall, Mundtrockenheit, Hypotonie; Insomnia; Übelkeit; Schläfrigkeit / Benommenheit; Probleme beim Wasserlassen; Erbrechen; Tod, Selbstmord und Suizidalität) **Ergebnisse (basierend auf 22 eingeschlossenen RCTs):** • Es zeigte sich ein stat. signifikanter Vorteil unter Escitalopram gegenüber Citalopram hinsichtlich dem akuten Ansprechen (OR 0.67, 95% KI 0.50 - 0.87) und der Remission (OR 0.53, 95% KI 0.30 - 0.93) • Stat. signifikant weniger Patienten in der Escitalopram Gruppe brachen die Studie aufgrund jeglicher Ursache ab, wenn verglichen wurde gegen Duloxetin (OR 0.62, 95% KI: 0.38 - 0.99). <u>Fazit der Autoren:</u> *'Some statistically significant differences favouring escitalopram over other antidepressive agents for the acute phase treatment of major depression were found, in terms of efficacy (citalopram and fluoxetine) and acceptability (duloxetine). There is insufficient evidence to detect a difference between escitalopram and other antidepressants in early response to treatment (after two weeks of treatment). Cost-effectiveness information is also needed in the field of antidepressant trials. Furthermore, as with most standard systematic reviews, the findings rely on evidence from direct comparisons. The potential for overestimation of treatment effect due to sponsorship bias should also be borne in mind.'* **Anmerkungen der Autoren und FBMed:** • Teilweise keine Angaben in den Studien zur Qualität, insbesondere zur Randomisierungsprozedur und dem Allocation Concealment. • Teilweise hohe Rate an Studienabbrechern in den Studien (> 30%)
Watanabe et al. 2011: Mirtazapine versus other antidepressive agents for depression.	Systematische Literaturrecherche bis 2011. **Population:** Erwachsene Patienten (>18 Jahre) mit unipolarer Depression **Vergleiche:** Mirtazapin vs. konventionelle trizyklische Antidepressiva, heterozyklische Mittel (z.B. Maprotilin), SSRIs, SNRIs; neuere Antidepressiva (MAOIs oder neuere Mittel wie Bupropion, Reboxetin); nicht-konventionelle Antidepressiva (z.B. pflanzliche Produkte) **Endpunkte:** o <u>Primärer Endpunkt</u>: Ansprechen o <u>Sekundäre Endpunkte</u>: Remission, Schwere der Depression, soziales Funktionieren, gesundheitsbezogene Lebensqualität, Verträglichkeit und Nebenwirkungen **Ergebnisse (basierend auf 29 Studien mit insgesamt 4974 Patienten):** **Wirksamkeit:** <u>Mirtazapin vs. trizyklische Antidepressiva:</u> o Wenn Mirtazapin gegenüber trizyklische Antidepressiva verglichen wurde (10 Studien mit insgesamt 1553 Patienten), zeigte sich kein stat. signifikanter Unterschied hinsichtlich dem Ansprechen nach 2 Wochen (OR: 0.85, 95% KI: 0.64 - 1.13) bzw. am Ende der akuten

	Behandlungsphase (nach 6-12 Wochen) (OR: 0.89, 95% KI 0.72 - 1.10). o Keine Angaben zu den anderen Endpunkten. <u>Mirtazapin vs. SSRIs:</u> o Wenn Mirtazapin gegenüber SSRIs verglichen wurde (12 Studien, N = 2626), zeigte sich ein stat. signifikanter Vorteil hinsichtlich dem primären Endpunkt nach zwei Wochen (OR 1.57, 95%KI: 1.30 - 1.88) und am Ender der akuten Behandlungsphase (OR: 1.19, 95% KI: 1.01-1.39), sowie der Remission nach 2 Wochen (OR: 1.82, 95%KI: 1.36 - 2.44, P < 0.0001, basierend auf 12 Studien); nicht aber am Ende der akuten Behandlungsphase bzw. der fortgeführten Behandlungsphase. Es zeigte sich kein stat. signifikanter Unterschied zwischen den Substanzen am Ende der fortführenden Behandlung (nach 24 Wochen) (basierend auf einer Studie; OR: 1.60, 95%KI 0.91- 2.81). o Keine Angaben zu den anderen Wirksamkeitsendpunkten. <u>Mirtazapin vs. SNRIs:</u> o Stat. signifikanter Vorteil unter Mirtazapin hinsichtlich dem primären Endpunkt nach 2 Wochen (nur gegen Venlafaxin OR: 2.29, 95% KI 1.45 - 3.59; basierend auf 2 Studien mit N = 415) und am Ende der akuten Behandlungsphase (OR: 1.53, 95% KI: 1.03 - 2.25), sowie der Remission nach 2 Wochen (OR: 2.34, 95% KI 1.07 - 5.13, p = 0.03, basierend auf 2 Studien). o Keine Angaben zu den anderen Zeit- bzw. Endpunkten. <u>Mirtazapine vs. heterozyklische Mittel:</u> o Keine stat. signifikanten Unterschiede hinsichtlich dem primären Endpunkt und der Remission. o Keine Angaben zu den anderen Wirksamkeitsendpunkten. <u>Mirtazapine versus newer antidepressants:</u> o Keine stat. signifikanten Unterschiede hinsichtlich des primären Endpunkts, der Remission und der Schwere der Depression. o Keine Angaben zu den anderen Wirksamkeitsendpunkten. **Sicherheit:** <u>Mirtazapin vs. trizyklische Antidepressiva:</u> o Stat. signifikant weniger Risiko unter Mirtazapin auf das Auftreten einer Hypertension oder Tachykardie (OR: 0.44, 95% KI 0.24- 0.81, p = 0.008, basierend auf 4 Studien) und Tremor (basierend auf 7 Studien; OR: 0.36, 95% KI 0.22 - 0.57, p < 0.0001). o Hinsichtlich der Studienabbrecher zeigten sich keine stat. signifikanten Unterschiede zwischen Mirtazapin und den anderen Antidepressiva. o Unter Mirtazapin zeigte sich ein erhöhtes Hungergefühl und Schläfrigkeit, sowie eine Gewichtszunahme gegenüber SSRIs, bei jedoch einem reduzierten Auftreten von Übelkeit, Erbrechen und einer Sexualdysfunktion. <u>Mirtazapin vs. SSRIs</u>: o Stat. signifikant höheres Risiko unter Mirtazapin hinsichtlich der Parameter: trockener Mund (basierend auf 10 Studien; OR: 1.80, 95%KI:1.37 - 2.36, p < 0.0001); Gewichtszunahme oder vermehrtes Hungergefühl (basierend auf 11 Studien: OR: 4.23, 95%KI: 2.93 - 6.11, p < 0.00001); Fatigue (basierend auf 8 Studien; OR: 1.53, 95%KI 1.08 - 2.15, p = 0.02); Schläfrigkeit (basierend auf 11 Studien; OR: 1.81,95% KI: 1.39 - 2.37, p < 0.0001). o Stat. signifikant weniger Risiko unter Mirtazapin hinsichtlich der Parameter: Schwitzen (basierend auf 5 Studien; OR: 0.25, 95% KI 0.15 - 0.44, p <0.00001); Durchfall (basierend auf 8 Studien; OR: 0.57, 95% KI: 0.41 - 0.80, p = 0.001); Übelkeit oder Erbrechen (basierend auf 11 Studien; OR: 0.33, 95% KI: 0.26 - 0.43, p < 0.00001); Sexualdysfunktion (basierend auf 4 Studien; OR: 0.31, 95% KI: 0.13 - 0.74, p= 0.009), Kopfschmerz (basierend auf 11 Studien; OR: 0.69,95% KI: 0.56 - 0.86, p = 0.0008). Tremor (basierend auf 5 Studien; OR: 0.34, 95%KI: 0.18 - 0.66, p = 0.001), und Schlafstörungen (basierend auf 5 Studien; OR:

	0.52, 95% KI 0.31 - 0.86, p= 0.01). Mirtazapin vs. SNRIs: o Stat. signifikanter Vorteil unter Mirtazapin hinsichtlich der Studienabbrüche aufgrund jeglicher Ursache (basierend auf 2 Studien zu Venlafaxin; OR: 0.65, 95% KI: 0.43 - 0.99, p = 0.04) während der akuten Behandlungsphase. o Stat. signifikant höheres Risiko unter Mirtazapin hinsichtlich einer Fatigue (basierend auf einer Studie; OR: 2.43, 95% KI 1.30 - 4.55, p = 0.006). o Stat. signifikant geringeres Risiko unter Mirtazapin hinsichtlich der Parameter: Schwitzen (basierend auf einer Studie; OR: 0.03, 95% KI: 0.00 - 0.45, p = 0.01), Konstipation (basierend auf einer Studie; OR: 0.22, 95% KI 0.06 - 0.83, p = 0.02) oder Schlafstörungen (basierend auf einer Studie; OR: 0.02, 95% KI: 0.0 - 0.41, p = 0.01). Mirtazapin vs. heterozyklische Mittel: o Wenn Mirtazapin gegen Trazodon verglichen wurde (einziger Vergleich), zeigte sich ein stat. signifikanter Vorteil unter Mirtazapin hinsichtlich dem Risiko auf Bluthochdruck oder Bradykardie (OR: 0.17, 95% KI: 0.03 - 1.00, p= 0.05). Mirtazapin vs. neuere Antidepressiva: Keine Angaben bzw. Ergebnisse heterogen. Fazit der Autoren: *'Some statistically significant and possibly clinically meaningful differences between mirtazapine and other antidepressive agents were found for the acute-phase treatment of major depression. Mirtazapine is likely to have a faster onset of action than SSRIs during the acute-phase treatment. Dropouts occur similarly in participants treated with mirtazapine and those treated with other antidepressants, although the adverse event profile of mirtazapine is unique.'* **Anmerkungen der Autoren und FBMed:** • Keine Studie machte Angaben zur Randomisierungssequenz und dem Allocation Concealment. • Viele Studien waren nur von kurzer Dauer (6 Wochen) • Teilweise wenige Studien zu den einzelnenVergleichen
Omori et al. 2010: Fluvoxamine versus other anti-depressive agents for depression	Systematische Literaturrecherche bis 2008 **Population:** Erwachsene Patienten (>18 Jahre) mit Depression **Vergleiche:** Fluvoxamin vs. andere Antidepressiva (inkl. konventionelle trizyklische Antidepressiva, heterozyklische Mittel (z.B. Maprotilin), SSRIs (Fluoxetin, Fluvoxamin, Citalopram, Paroxetin, Escitalopram), neuere Antidepressiva (SNRIs wie Venlafaxin, Duloxetin, Milnacipran); MAOIs oder neuere Arzneimittel wie Mirtazapin, Bupropion, Reboxetin; und nicht-konventionelle Antidepressiva (z.B. pflanzliche Produkte) **Endpunkte:** • Primärer Endpunkt: Ansprechen in der akuten Behandlungsphase • Sekundäre Endpunkte: Ansprechen in weiteren Behandlungsphasen, Remission (Phasen), Veränderung auf der Depressionsskala am Ende der Studie, Lebensqualität, soziales Funktionieren, Kosten, Verträglichkeit, Dropout (allgemein, aufgrund von Nebenwirkungen, aufgrund von Unwirksamkeit), Nebenwirkungen (Anzahl Patienten die mind. 1 Nebenwirkungen erfuhren), spezifische Nebenwirkungen **Ergebnisse (basierend auf 54 Studien mit N=5122):** • Hinsichtlich der Wirksamkeit zeigten sich keine eindeutige Über- oder Unterlegenheit von Fluvoxamin gegenüber den anderen Antidepressiva hinsichtlich des Ansprechens, der Remission und der Verträglichkeit.

	• Dennoch zeigten sich Unterschiede hinsichtlich der Nebenwirkungsprofile. Insbesondere für gastrointestinale Ereignisse zeigte sich ein Nachteil unter Fluvoxamin: Übelkeit/Erbrechen (vs. Imipramin: OR: 2.23, KI: 1.59 - 3.14; vs. Clomipramin: OR: 2.13, KI 1.06 - 4.27; vs. Amitriptylin: OR: 2.86, KI 1.31 - 2.63). Fazit der Autoren: *'We found no strong evidence that fluvoxamine was either superior or inferior to any other antidepressants in terms of efficacy and tolerability in the acute phase treatment of depression. However, differing side effect profiles were evident. Based on these findings, we conclude that clinicians should focus on practical or clinically relevant considerations, including these differences in side effect profiles.'* **Anmerkungen der Autoren und FBMed:** • Viele Studien waren klein (<100 Patienten) • Fehlende Angaben zur Qualität (z.B. Randomisierung, Allocation Concealment etc.) • Teilweise hohe Studienabbruchrate (>20%)
Candy et al. 2008: Psychostimulants (PS) for depression	Systematische Literaturrecherche. Recherche im Jahr 2006. Ende des Suchzeitraumes nicht angegeben. **Population:** Erwachsene Patienten mit Depression (jede Form) **Vergleiche:** PS vs. Antidepressiva **Endpunkte:** • Primäre Endpunkte: Therapieansprechen anhand HAM-D oder MADRS oder anderer validierter Depressionsskala (als kontinuierlicher Endpunkt oder dichotomer Endpunkt [50% oder weniger]) • Sekundäre Endpunkte: Veränderung der Symptome (wie: Gewicht, Schlafverhalten, Appetitverhalten, Fatigue etc.), Remission, soziales Funktionieren, Verträglichkeit, Nebenwirkungen *Hinweis*: Endpunkte wurden nach Länge der Behandlung dargestellt: Kurzzeit (4 Wochen oder weniger), mittelfristig (5 bis 12 Wochen), Langzeit (13 Wochen oder länger) **Ergebnisse:** *Hinweis:* Ergebnisdarstellung fokussiert sich auf direkte Vergleiche zwischen den Arzneimitteln PS vs. andere Antidepressiva (basierend auf 2 Studien): • Reduktion der Depressionssymptomatik: Keine stat. signifikanten Unterschiede zwischen den Substanzen • Verträglichkeit: Keine stat. signifikanten Unterschiede zwischen den Substanzen. • Daten zu anderen sekundären Endpunkten lagen für diesen Vergleich nicht vor. Fazit der Autoren: *'There is some evidence that in the short-term, PS reduce symptoms of depression. Whilst this reduction is statistically significant, the clinical significance is less clear. Larger high quality trials with longer follow-up and evaluation of tolerance and dependence are needed to test the robustness of these findings and, furthermore, to explore which PS may be more beneficial and in which clinical situations they are optimal.'* **Anmerkungen der Autoren und FBMed:** • Teils fehlende Angaben in den Studien zur Qualität, insbesondere zur Randomisierungsprozedur • Teilweise sehr kleine Studien • Keine Einschränkung auf eine bestimmte Form der Depression

	• In diesem Review wurden Patienten ab 16 Jahren als Erwachsene betrachtet • Zu dem direkten Vergleich lagen nur wenige Studien vor (hier 2 Studien)
Guaiana et al. 2007: Amitriptyline for depression.	Systematische Literaturrecherche im Jahr 2005. Ende des Suchzeitraumes nicht angegeben. **Population:** Patienten mit Depression (keine Alterseinschränkung) **Vergleiche:** Amitriptylin vs. ein anderes trizyklisches/ heterozyklisches Antidepressivum oder einem SSRI (Fluoxetin, Fluvoxamin, Sertralin, Paroxetin, Citalopram) **Endpunkte (dichotom und kontinuirlich[1,2]):** Therapieansprechen, Durchschnittswert der Gruppen am Ende der Studien auf der HAM-D oder der MADRS oder einer anderen Depressionsskala), Verträglichkeit, Nebenwirkungen **Ergebnisse (basierend auf 194 Studien):** **Wirksamkeit:** • Insgesamt sprachen stat. signifikant mehr Patienten auf eine Therapie mit Amitriptylin an, wenn verglichen wurde gegenüber einer anderen Gruppe von Antidepressiva (OR: 1.12; 95% KI:1.02 - 1.23). • Der Effekt hinsichtlich der Wirksamkeit unter Amitriptylin gegenüber anderen Antidepressiva anhand des kontinuierlichen Endpunktes zeigte ebenfalls einen stat. signifikanten Vorteil unter Amitriptylin (SMD: 0.13, 95% KI 0.04 - 0.23). o Wenn stratifiziert wurde nach AM-Klassen, zeigten sich keine stat. signifikanten Unterschiede hinsichtlich des Therapieansprechens zwischen Amitriptylin und den trizyklischen Antidepressiva oder SSRIs. o Wenn nach Studiensetting stratifiziert wurde, zeigte sich ein stat. signifikanter Vorteil hinsichtlich dem Therapieansprechen unter Amitriptylin gegenüber den anderen Antidepressiva bei stationär behandelten Patienten (OR: 1.22, 95% KI: 1.04 - 1.42); nicht aber bei ambulant behandelten Patienten. **Sicherheit** • Es zeigten sich vergleichbare Studienabbruchraten zwischen der Amitriptylin und der Kontrollgruppe, jedoch zeigte sich eine stat. signifikant geringere Anzahl an Patienten in den Kontrollarmen, die eine Nebenwirkung erfuhren (OR: 0.66, 95% KI: 0.59 - 0.74) o Wenn nach AM-Klassen stratifiziert wurde, zeigte sich ein stat. signifikanter Vorteil hinsichtlich der Studienabbruchrate unter SSRIs gegenüber Amitriptylin (OR: 0.84, 95% KI: 0.75 - 0.95). o Wenn nach Studiensetting stratifiziert wurde, zeigte sich eine stat. signifikant schlechtere Verträglichkeit unter Amitriptylin gegenüber den anderen Antidepressiva unter ambulant behandelten Patienten (OR: 0.90, 95% KI: 0.81-0.99); jedoch nicht unter stationär behandelten Patienten. Unter den stationär behandelten Patienten, zeigten sich keine Unterschiede zwischen Amitriptylin und den trizyklischen Antidepressiva oder SSRIs. Unter den ambulant behandelten Patienten, zeigte sich eine stat. signifikant schlechtere Verträglichkeit unter Amitriptylin gegenüber SSRIs (OR: 0.77, 95% KI 0.67 - 0.89); jedoch nicht gegenüber trizyklischen Antidepressiva. <u>Fazit der Autoren:</u> *'This present systematic review indicates that amitriptyline is at least as efficacious as other tricyclics or newer compounds. However, the burden of side-effects in patients receiving it was greater. In comparison with selective serotonin reuptake inhibitors amitriptyline was less well tolerated, and although counterbalanced by a higher proportion of responders, the difference was not statistical.'*

	Anmerkungen der Autoren und FBMed: • Ergebnisse zu den Studienabbrüchen sollten mit Vorsicht interpretiert werden, da in vielen Studien keine Angaben zu den Abbruchgründen gemacht wurde. • Die Qualität der Studien war sehr unterschiedlich. Die meisten Studien waren von moderate/schlechter Qualität. RCTs die Amitriptylin gegenüber trizyklische Antidepressiva verglichen haben wiesen eine schlechtere Qualität auf als Studien die Amitriptylin gegenüber SSRIs getestet haben. Ein möglicher Grund für diesen Unterschied kann der Publikationszeitpunkt sein (RCTs mit trizyklischen Antidepressiva sind älter; publiziert im Jahr 1960 und 1970). *[1]Dichotomous outcomes=Two reviewers independently extracted the number of patients undergoing the randomisation procedure, the number of patients who failed to complete the study and that of patients complaining side-effects. The number of improved patients was extracted in agreement with the definition of responders adopted in the primary studies. When authors did not report any definition of responders, the number of patients showing a 50% reduction in the HMD or MADRS scale was extracted; if these figures were not available, we extracted the number of patients categorised as "much improved" and "improved" at the Clinical Global Impression (CGI), or the number of patients in the corresponding categories at any other rating scale.* *[2]Continuous outcomes= The mean scores at endpoint, the standard deviation (SD) or standard error (SE) of these values, and the number of patients included in these analyses, were extracted. Data were extracted from the HMD. If this scale was not available, data were extracted from the MADRS. If both the HMD and MADRS were not available, data were extracted from any other depression scale.*
Cipriani et al. 2005: Fluoxetine versus other types of pharmacotherapy for depression *Hinweis: Veralteter Review*	Systematische Literaturrecherche bis 2004 **Population:** Patienten mit Depression (keine Altersbeschränkung angegeben) **Vergleiche:** Fluoxetin vs. trizyklische/heterozyklische Antidepressiva, SSRIs (Fluoxetin, Fluvoxamin, Sertralin, Paroxetin, Citalopram), neueren Mitteln oder pflanzlichen Produkten (z.B. Hyperikum) **Endpunkte (dichotom und kontinuirlich[1,2]):** Therapieansprechen, Durchschnittswert der Gruppen am Ende der Studien der HAM-D oder der MADRS oder einer anderen Depressionsskala, Verträglichkeit, Nebenwirkungen **Ergebnisse:** • Keine stat. signifikanten Unterschiede zwischen den AM-Gruppen hinsichtlich des Therapieansprechens (dichotomer Endpunkt). Wenn Head-to-Head verglichen wurde, zeigte sich ein stat. signifikanter Nachteil unter Fluoxetin gegenüber Dothiepin (OR: 2.09, 95% KI: 1.08 - 4.05), Sertralin (OR: 1.40, 95% KI: 1.11 - 1.76), Mirtrazapin (OR: 1.64, 95% KI: 1.01 - 2.65), und Venlafaxin (OR: 1.40, 95% KI: 1.15 - 1.70). • Hinsichtlich des kontinuierlichen Endpunktes, zeigte sich ein stat. signifikanter Vorteil unter Fluoxetin gegenüber ABT-200 (SMD: - 1.85, 95%KI: - 2.25; - 1.45) und Milnacipram (SMD: - 0.38, 95% KI: - 0.71; - 0.06). Gegensätzlich zeigte sich ein stat. signifikanter Nachteil unter Fluoxetin gegenüber Venlafaxin (SMD: 0.11, 95% KI: 0.00-0.23). • Fluoxetin ist besser verträglich, wenn gegenüber trizyklische Antidepressiva (als Gruppe) getestet wurde (OR: 0.78, 95% KI: 0.68 - 0.89). Dieser stat. signifikante Vorteil zeigte sich auch wenn gegenüber

	individuelle Antidepressiva getestet wurde (Amitriptylin→OR: 0.64, 95% KI: 0.47 - 0.85; Imipramin→OR: 0.79, 95% KI: 0.63 - 0.99; ABT-200→OR: 0.21, 95% KI: 0.10 - 0.41), Pramipexol→OR: 0.20, 95% KI: 0.08 - 0.47) und Reboxetin→OR: 0.61, 95% KI: 0.40 - 0.94). Fazit der Autoren: *'There are statistically significant differences in terms of efficacy and tolerability between fluoxetine and certain ADs, but the clinical meaning of these differences is uncertain, and no definitive implications for clinical practice can be drawn. From a clinical point of view the analysis of antidepressants' safety profile (adverse effect and suicide risk) remains of crucial importance and more reliable data about these outcomes are needed. Waiting for more robust evidence, treatment decisions should be based on considerations of clinical history, drug toxicity, patient acceptability, and cost.We need for large, pragmatic trials, enrolling heterogeneous populations of patients with depression to generate clinically relevant information on the benefits and harms of competitive pharmacological options. A meta-analysis of individual patient data from the randomised trials is clearly necessary.'* **Anmerkungen der Autoren und FBMed:** • Es wurden verschiede Studientypen gepoolt [1] *Dichotomous outcomes= The number of patients undergoing the randomisation procedure, the number of patients who failed to complete the study – because of side effects, inefficacy and any cause - were recorded. The number of patients showing a reduction of at least 50% at the HDRS was extracted.* [2] *Continuous outcomes= The mean scores at endpoint, the standard deviation (SD) or standard error (SE) of these values, and the number of patients included in these analyses, were extracted. Data were extracted from the HDRS or MADRS or any depression scale.*
Magni et al. 2013: Fluoxetine versus other types of pharmacotherapy for depression	--- Population, Intervention/Komparator, Endpunkte siehe Cipriani et al. (2005). Systematische Literaturrecherche bis Mai 2012. Ergebnisse: A total of 171 studies were included (24,868 participants). Studies had homogenous characteristics in terms of design, intervention and outcome measures. • 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) (OR: 0.97, 95% CI 0.77 to 1.22; 24 RCTs, 2124 participants) and a continuous outcome (mean scores at the end of the trial or change score on depression measures) (SMD: 0.03, 95% CI -0.07 to 0.14; 50 RCTs, 3393 participants). • On a dichotomous outcome, fluoxetine was less effective than dothiepin or dosulepin (OR: 2.13, 95% CI 1.08 to 4.20; 95% CI 3 to 50; 2 RCTs, 144 participants), sertraline (OR: 1.37, 95% CI 1.08 to 1.74; 95% CI 7 to 58; 6 RCTs, 1188 participants), mirtazapine (OR: 1.46, 95% CI 1.04 to 2.04; 95% CI 6 to 134; 4 RCTs, 600 participants) and venlafaxine (OR: 1.29, 95% CI 1.10 to 1.51;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; 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; 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; 95% CI 2 to 5; 1 RCT, 144 participants), pramipexole (total dropout OR: 0.12, 95% CI 0.03 to 0.42, 95% CI 2 to 5; 1 RCT, 105 participants), and reboxetine (total dropout OR: 0.60, 95% CI 0.44 to 0.82, 95% CI 6 to 24; 4 RCTs, 764 participants). <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. <u>Fazit der Autoren</u>*: 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.*

Guaiana et al. 2013: Agomelatine versus other antidepressive agents for major depression.	**Zielsetzung:** 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, and, 3) to investigate the adverse effects of agomelatine, including the general prevalence of side effects in adults. ➔ Systematische Literaturrecherche bis Juli 2013 **Population:** Participants, aged 18 years or older, with a primary diagnosis of major depression. **Vergleiche:** 1. Selective serotonin reuptake inhibitors (fluoxetine, fluvoxamine, citalopram, paroxetine, escitalopram) 2. Serotonin-norepinephrine reuptake inhibitors (venlafaxine, duloxetine, milnacipran) 3. 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). *Of note: No restrictions regarding dose, frequency, intensity or duration.Tials were excluded in which agomelatine was used as an augmentation strategy.* **Endpunkte:** Primärer Endpunkt: The number of participants who responded to treatment, showing a reduction of at least 50% on the HAM-D, the MADRS, or any other depression scale Sekundäre Endpunkte: The number of participants who achieved remission as defined by: a score of 7 or less on the 17-item HAM-D, or 8 or less on the longer version of HAM-D; 10 or less on the MADRS; 'not ill or borderline mentally ill' on the CGI-S; or any other equivalent value on a depression scale defined by the authors; Nebenwirkungen **Ergebnisse:** Allgemein: A total of 13 studies (4495 participants) were included. 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. • Agomelatine showed no advantage or disadvantage over other antidepressants for remission. • There was no evidence that agomelatine was associated with a higher drop-out rate due to inefficacy than SSRIs as a hole. 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 = 0.0005), and showed the same level of tolerability as SSRIs (RR: 0.95; 95% CI 0.83 to 1.09, P = 0.44). • Agomelatine induced a lower rate of dizziness than venlafaxine (RR: 0.19, 95% CI 0.06 to 0.64, P = 0.007) ➔ No studies were found comparing agomelatine with tricyclic or heterocyclic antidepressants, MAOIs, newer agents (mirtazapine, bupropion, reboxetine), atypical antipsychotics in monotherapy (risperidone, paliperidone, olanzapine, quetiapine, aripiprazole, amisulpride, ziprasidone) or non-conventional antidepressive agents (herbal products such as Hypericum).

	Qualität der zugrundeliegenden Studien: • 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. • With regard to precision, the efficacy outcomes were precise, but the tolerability outcomes were mostly imprecise. • Publication bias was variable and depended on the outcome of the trial. • 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, and some of these were unpublished. 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.*

Systematische Reviews

Cipriani et al. 2009: Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis.	Systematische Literarturrecherche bis 2007. Indirekter Vergleich basierend auf einer Netzwerkanalyse. **Population:** Erwachsene Patienten mit majorer Depression **Vergleich:** Es wurden folgende Antidepressiva verglichen: Bupropion, Citalopram, Duloxetin, Escitalopram, Fluoxetin, Fluvoxamin, Milnacipran, Mirtazapin, Paroxetin, Reboxetin, Sertralin, und Venlafaxin. **Endpunkte:** Therapieansprechen, Studienabbrecher **Ergebnisse** (basierend auf 117 RCTs mit insgesamt 25928 Patienten): <u>Wirksamkeit</u>: • Es zeigte sich ein stat. signifikanter Vorteil unter Mirtazapin, Escitalopram, Venlafaxin, und Sertralin (darunter weniger deutliche Wirksamkeit unter Sertralin gegenüber den anderen), wenn verglichen wurde gegenüber Duloxetin (ORs:1.39, 1.33, 1.30 und 1.27), Fluoxetin (ORs: 1.37, 1.32, 1.28, und 1.25), Fluvoxamin (1.41, 1.35, 1.30, und 1.27), Paroxetin (ORs: 1.35, 1.30, 1.27, und 1.22), und Reboxetin (ORs: 2.03, 1.95, 1.89, und 1.85). • Reboxetin zeigte eine stat. signifikant geringere Wirksamkeit, verglichen mit allen anderen Antidepressiva. <u>Sicherheit:</u> • Es zeigte sich eine schlechtere Verträglichkeit unter Duloxetin und Paroxetin, wenn gegenüber Escitalopram und Sertralin verglichen wurde. • Desweiteren zeigte sich eine schlechtere Verträglichkeit unter o Fluvoxamin gegenüber Citalopram, Escitalopram und Sertralin; o unter Venlafaxin gegenüber Escitalopram; und o unter Doluxetin, Fluvoxamin, Paroxetin und Reboxetin gegenüber Escitalopram und Sertralin. **Basierend auf dem indirekten Vergleich, wurde eine 'ranking' vorgenommen:** • Mirtazapin, Escitalopram, Venlafaxin, und Sertralin wurden als die wirksamsten Therapieoptionen eingeschätzt; Escitalopram, Sertralin, Bupropion, und Citalopram hingegen wurden als die verträglichsten Therapieoptionen eingestuft. <u>Fazit der Autoren:</u> *'Clinically important differences exist between commonly prescribed antidepressants for both efficacy and acceptability in favour of escitalopram and sertraline. Sertraline might be the best choice when starting treatment for moderate to severe major depression in adults because it has the most favourable balance between benefits, acceptability, and acquisition cost.'* **Kommentare der Autoren und FBMed:** • Ergebnisse basieren auf einem indirekten Vergleich • Keine Angaben zu Endpunkten wie: Nebenwirkungen, Lebensqualität etc. • Nicht alle Studien machten Angaben zur Randomisierungsprozedur oder dem Allocation concealment. • Studien waren zwei-, oder dreiarmig bzw. hatten mehr als drei Arme • Nur 14 Studien wiesen eine Nachbeobachtungsdauer auf von >12 Wochen auf.
Ramsberg et al. 2012: Effectiveness and Cost-Effectiveness of	Systematische Literaturrecherche mit Metaanalyse basierend auf direkt und indirekt vergleichender Evidenz. Suchzeitraum nicht angegeben.

Antidepressants in Primary Care: A Multiple Treatment Comparison Meta-Analysis and Cost-Effectiveness Model.	**Population:** Patienten mit moderater oder schwerer Depression **Vergleich:** 10 Antidepressiva wurden miteinander verglichen: Citalopram, Duloxetin, Escitalopram, Fluoxetin, Fluvoxamin, Mirtazapin, Paroxetin, Reboxetin, Sertralin und Venlafaxin **Endpunkte:** Remission **Ergebnisse:** • Escitalopram wies eine stat. signifikant höhere Wahrscheinlichkeit auf hinsichtlich dem Erreichen einer Remission, wenn verglichen wurde gegenüber Amitriptylin, Citalopram, Fluoxetin, Fluvoxamin, Paroxetin, und Sertralin → basierend auf indirekter Evidenz; heterogene Ergebnisse auf Basis direkt vergleichender Studien (keine Unterschiede wenn Escitalopram gegenüber Paroxetin; bleibender Vorteil unter Escitalopram wenn gegen Citalopram getestet wurde; zu den anderen oben indirekten Vergleichen lagen keine direkt vergleichenden Studien vor bzw. wurde kein Unterschied identifiziert). • Desweiteren zeigten sich stat. signifikante Vorteile basierend auf indirekt vergleichender Evidenz unter: o Mirtazapin, Paroxetin, wenn gegenüber Fluoxetin verglichen wurde o Venlafaxin, wenn gegen Citalopram getestet wurde o Duloxetin und Venlafaxin, wenn gegenüber Fluoxetin und Fluoxamin untersucht wurde. • Auch hier waren die Ergebnisse zum Teil heterogen, wenn direkt vergleichende Studien betrachtet wurden. Es zeigte sich weiterhin ein stat. signifikanter Vorteil unter Venlafaxin gegenüber Fluoxetin; nicht aber wenn Mirtazapin gegenüber Fluoxetin verglichen wurde. Zu den verbleibenden indirekten Vergleichen lagen keine direkt vergleichenden Studien vor bzw. wurde kein Unterschied identifiziert. Fazit der Autoren: *'Of the investigated antidepressants, escitalopram has the highest probability of remission and is the most effective…'* **Anmerkungen der Autoren oder FBMed:** • Ergebnisse basieren teilweise auf einem indirekten Vergleich • U.a. Studien eingeschlossen mit einer Dauer von 6 Wochen→ möglicherweise zu kurz für die Beurteilung einer Remission • Die meisten Studien waren von der Industrie gesponsert
Montgomery et al. 2011: Efficacy of Escitalopram compared to Citalopram: a meta-analysis.	Systematische Literaturrecherche bis 2009 mit Metaanalyse. **Population**: Patienten mit majorer Depression **Vergleich**: Escitalopram vs. Citalopram **Endpunkte**: • Primärer Endpunkt: Unterschied auf der MARDS Skala nach 8 Wochen • Sekundärer Endpunkt: Therapieansprechen (≥ 50% Verbesserung zu Baseline), Remission (MADRS ≤12) **Ergebnisse** (basierend auf 9 Studien mit insgesamt 2009 Patienten): • Insgesamt zeigte sich ein stat. signifikanter Behandlungseffekt zugunsten von Escitalopram, verglichen mit Citalopram hinsichtlich eines Unterschiedes nach 8 Wochen auf der MADRS (Unterschied: 1.7 Punkte; 95%KI: 0.8-2.6; p=0.0002), des Therapieansprechens (8.3 Prozentpunkte; 95%KI: 4.4-12.3) und der Remission (1.86; 95%KI: 12.1-23.1). Fazit der Autoren: *'In this meta-analysis, the statistically significant superior efficacy of escitalopram compared to citalopram was shown to be clinically relevant.'* **Anmerkungen der Autoren und FBMed:** • Viele Studien waren Industrie gesponsert.

Trkulja 2010: Is Escitalopram Really Relevantly Superior to Citalopram in Treatment of Major Depressive Disorder? A Meta-analysis of Head-to head Randomized Trials.	Systematische Literaturrecherche bis 2009 mit Metaanalyse. **Population**: Patienten mit majorer Depression **Vergleich**: Escitalopram vs. Citalopram **Endpunkte:** MADRS (zu Woche 1, 4,6,8 und 24), Therapieansprechen (zu Woche 2,4,6,8 und 24), Reduktion hinsichtlich des clinical global impression-severity (CGI-S) (zu Woche 6,8 und 24), Studienabbrüche aufgrund von Nebenwirkungen oder Unwirksamkeit (Kurzzeitbehandlung bis 8 Wochen und mittelfristig bis 24 Wochen). **Ergebnisse:** • MADRS: MADRS reduction was greater with escitalopram, but 95% confidence intervals (CI) around the mean difference were entirely or largely below 2 scale points (minimally important difference) and CI around the effect size (ES) was below 0.32 ("small") at all time points. • Response: Risk of response was higher with escitalopram at week 8 (relative risk, 1.14; 95% CI, 1.04 to 1.26) but number needed to treat was 14 (95% CI, 7 to 111). • CGI-S: All 95% CIs around the mean difference and ES of CGI-S reduction at week 8 were below 0.32 points and the limit of "small," respectively. Data for severe patients (MADRS≥30) are scarce (only 1 RCT), indicating somewhat greater efficacy (response rate and MADRS reduction at week 8, but not CGI-S reduction) of escitalopram, but without compelling evidence of clinically relevant differences. • Discontinuations due to adverse events: Discontinuations due to adverse events or inefficacy up to 8 weeks of treatment were comparable. Data for the period up to 24 weeks are scarce and inconclusive. Fazit der Autoren: '*Presently, the claims about clinically relevant superiority of escitalopram over citalopram in short-to-medium term treatment of major depressive disorder are not supported by evidence.*' **Anmerkungen der Autoren oder FBMed:** • Teilweise kurze und kleine Studien • Kleine Effekte ('small effect size')
Gartlehner et al. 2011: Comparative Benefits and Harms of Second-Generation Antidepressants for Treating Major Depressive Disorder: An Updated Meta-analysis.	Systematische Literaturrecherche bis 2011 mit Metaanalyse und indirekten Vergleichen. **Population**: Erwachsene Patienten mit majorer Depression **Vergleich**: Vergleich verschiedener Zweitgenerationsantidepressiva untereinander **Endpunkte**: Therapieansprechen, Lebensqualität, Nebenwirkungen **Ergebnisse** (basierend auf 234 Studien von guter oder moderater Qualität; darunter 118 head-to-head RCTs): Wirksamkeit für die akute Behandlungsphase (Hea-to-Head Studien von guter oder moderater Qualität mit insgesamt 20000 Patienten): Diese Studien wiesen direkte Evidenz auf für 40 von 78 möglichen Vergleichen zwischen den Substanzen. Diese direkte Evidenz reichte aus um eine Metaanalyse für 6 Substanzen durchzuführen. Zusätzlich wurden mixed treatment comparisons (indirekte Vergleiche) für alle möglichen Vergleiche hinsichtlich dem Endpunkt Therapieansprechen durchgeführt • Insgesamt waren die Effekte zwischen den Substanzen vergleichbar. Es zeigten sich zwar teilweise stat. signifikante Unterschiede zwischen den Therapiearmen, allerdings war das Ausmaß des Unterschiedes nur mäßig ('modest') und möglicherweise nicht klinisch relevant (*Hinweis: Aussage der Autoren*). • Wenn SSRIs gegeneinander getestet wurden zeigten sich folgende stat. signifikanten Unterschiede hinsichtlich des Therapieansprechens:

	o Nachteil unter Citalopram verglichen mit Escitalopram (OR: 1.49; 95% KI: 1.07 - 2.01; basierend auf einer unpublizierten Studie und 5 direkt publizierten, direkt vergleichenden Studien mit insgesamt 1802 Patienten), o Vorteil unter Escitalopram vs. Fluoxetin (OR: 0.66; 95%KI: 0.49–0.89; basierend auf indirekten Vergleichen mit 2/62 Studien), o Nachteil unter Fluoxetin verglichen mit Sertraline (OR: 1.42; KI, 1.08 -1.85; basierend auf 4 direkt vergleichenden Studien mit insgesamt 960 Patienten) • Keine stat. signifikanten Unterschiede zwischen den anderen SSRIs, wenn diese gegeneinander getestet wurden. • Wenn SSRIs gegenüber SNRIs bzw. SNRIs untereinander verglichen wurden, zeigten sich folgende stat. signifikanten Unterschiede hinsichtlich des Therapieansprechens: o Vorteile unter Escitalopram gegenüber Duloxetin (OR: 0.74; 95%KI: 0.56-0.98; basierend auf einem indirekten Vergleich mit 3/61 Studien) o Nachteil unter Fluoxetin gegenüber Venlafaxin (OR: 1.47; 95%KI: 1.16–1.86; basierend auf Metaanalyse von 5 direkt vergleichenden Studien) • Keine stat. signifikanten Unterschiede zwischen den anderen SSRIs gegenüber SNRIs bzw. SNRIs untereinander. • Wenn SSRIs gegenüber anderen Zweitgenerationsantidepressiva verglichen wurden, zeigten sich Keine stat. signifikanten Unterschiede • Lebensqualität: 17 Studien mit insgesamt 3960 Patienten zeigten keinen stat. signifikanten Unterschied hinsichtlich der Lebensqualität. **Sicherheitsprofil:** Unerwünschte Ereignisse allgemein**:** Insgesamt betrachtet waren die Nebenwirkungen unter Zweitgenerationsantidepressiva ähnlich. Sie unterschieden sich jedoch hinsichtlich einiger spezifischer Nebenwirkungen wie: **siehe Anlage 2** Studienabbrüche allgemein: Insgesamt zeigten sich vergleichbare Studienabbrüche zwischen SSRIs und anderen Zweitgenerationsantidepressiva (Range: 15% - 25%). Duloxetin zeigte ein 67%ig (KI: 17% - 139%) und Venlafaxin ein 40%ig (KI: 16% - 73%) höheres Risiko auf einen Studienabbruch aufgrund von Nebenwirkungen, verglichen mit SSRIs als Klasse. Studienabbrüche aufgrund von fehlender Wirksamkeit war ebenfalls vergleichbar zwischen SSRIs und anderen Zweitgenerationsantidepressiva, mit Ausnahme von Venlafaxin. o Venlafaxin zeigte ein 34%ig geringeres Risiko auf einen Studienabbruch aufgrund von fehlender Wirksamkeit, verglichen mit SSRIs als Klasse. Schwere unerwünschte Ereignisse: Es lagen lediglich (verwertbare) Daten hinsichtlich einer sexuellen Dysfunktion vor. Es zeigte sich eine geringere Rate an sexueller Dysfunktion unter Bupropion, wenn verglichen wurde gegenüber Escitalopram, Fluoxetin, Paroxetin, und Sertralin (basierend auf 5 Studien mit insgesamt 2399 Patienten). Verglichen mit anderen Zweitgenerationsantidepressiva, wies Paroxetin höhere Raten an sexueller Dysfunktion auf. Diese Unterschiede waren aber nicht immer stat. signifikant. Fazit der Autoren: *'Current evidence does not warrant recommending a particular second-generation antidepressant on the basis of differences in efficacy. Possible side effects, convenience of dosing regimens, and costs may best guide the choice of a second-generation antidepressant for treating major depression in adults, because these agents probably have similar efficacy.'*

	Anmerkungen der Autoren oder FBMed: • Es gelten die allgemeinen methodischen Einschränkungen eines indirekten Vergleiches • Teilweise sehr kurze oder kleine Studien.
Wolff et al. 2013: Selective serotonin reuptake inhibitors and tricyclic antidepressants in the acute treatment of chronic depression and dysthymia: A systematic review and meta-analysis.	Systematische Literaturrecherche (Ende des Suchzeitraums nicht angegeben) mit Metaanalyse. **Population:** Patienten mit einer chronischer Depression und Dysthymie **Vergleich (Fokus auf direkte Vergleiche zwischen den Substanzen):** SSRIs vs. trizyklische Antidepressiva **Endpunkte:** Therapieansprechen, Studienabbrüche **Ergebnisse** (basierend auf 20 Studien mit 22 relevanten Vergleichen): • Es zeigten sich keine stat. signifikanten Unterschiede zwischen SSRIs und trizyklische Antidepressiva hinsichtlich des Therapieansprechens (akute Behandlungsphase). • SSRIs zeigten stat. signifikante Vorteile hinsichtlich der Studienabbruchrate, wenn verglichen wurde gegenüber den trizyklischen Antidepressiva (OR: 0.41; p=0.02). Fazit der Autoren: *'This systematic review provides evidence for the efficacy of both SSRIs and TCAs in the treatment of chronic depression and showed a better acceptability of SSRIs.'* **Anmerkungen der Autoren und FBMed:** • Unklare methodische Qualität der Primärstudien. • Viele Studien untersuchten überwiegend Dysthymie-Patienten→ Übertragbarkeit
Van den Broek et al. 2009: Efficacy of venlafaxine compared with tricyclic antidepressants in depressive disorder: a meta-analysis. *Siehe auch: Bauer et al. 2009*	Systematische Literaturrecherche (Suchzeitraum nicht angegeben) mit Metaanalyse. **Population:** Patienten mit Depression **Vergleich:** Venlafaxin vs. einem trizyklischen Antidepressivum (TCA) **Endpunkte:** Therapieansprechen, Studienabbrüche (allgemein und aufgrund von Nebenwirkungen) **Ergebnisse (basierend auf 7 Studien):** *Vergleiche: Venlafaxin vs. Imipramin (3 Studien), Amitriptylin (2 Studien), Clomipramin (2 Studien).* • Insgesamt (gepooltes Ergebnis) zeigte sich kein stat. signifikanter Unterschied zwischen Venlafaxin und TCAs hinsichtlich der Wirksamkeit (Therapieansprechen) und der Verträglichkeit (Studienabbrüche allgemein und aufgrund von Nebenwirkungen). • Dies war auch bei allen Vergleichen zwischen Venlafaxin und individuellen TCAs der Fall, sofern der Endpunkt Studienabbrüche betrachtet wurde. • Es zeigte sich bei einem individuellen Vergleich zwischen Venlafaxin und Imipramin ein stat. signifikanter Vorteil unter Venlafaxin.
Machado et al. 2010: Comparison of SSRIs and SNRIs in major depressive disorder: a meta-analysis of head-to-head randomized clinical trials.	Systematische Literaturrecherche bis 2007 mit Metaanalyse. **Population:** Erwachsene Patienten mit majorer Depression **Vergleich:** SNRIs vs. SSRIs **Endpunkte:** Remission, Studienabbrüche (aufgrund von Nebenwirkungen oder fehlender Wirksamkeit) **Ergebnisse** (basierend auf 15 Studien mit insgesamt 3094 Patienten): • Wirksamkeit: Es zeigte sich ein nachteiliger Effekt hinsichtlich der Remission unter SSRIs, verglichen mit SNRIs (OR: 1.27; 95%KI: 1.06-1.52); die Remissionsraten lagen bei 48.5% (+/-3.2%) unter SNRIs und bei 41.9% (+/-4.2%) unter SSRIs (keine Heterogenität zwischen den

	Studien); der gepoolte Unterschied zwischen den Remissionsraten der beiden Substanzklassen lag bei 5.7% und war stat. signifikant (p=0.007). • Sicherheit: Studienabbrüche aufgrund von Nebenwirkungen war stat. signigikant höher unter SNRIs, verglichen mit SSRIs (3.2% Unterschied; p<0.001). Studienabbrüche aufgrund von fehlender Wirksamkeit zeigten keinen stat. signifikanten Unterschied zwischen den beiden Gruppen. Fazit der Autoren: *'Serotonin and norepinephrine reuptake inhibitors showed statistical but not clinical significance when compared with SSRIs in treating MDD.'* **Anmerkungen der Autoren und FBMed:** • Wenige Studien vorhanden • Generalisierbarkeit der individuellen Substanzen auf die Klasse (Klassen meist nur durch wenige Substanzen repräsentiert)
Kasper et al. 2013: Antidepressant efficacy of agomelatine versus SSRI/SNRI: results from a pooled analysis of head-to-head studies without a placebo control.	Systematische Literaturrecherche (Suchzeitraum nicht angegeben) mit Metaanalyse. **Population:** Patienten mit Depression **Vergleich:** Agomelatin vs. SSRIs und SNRIs **Endpunkte:** HAM-D Gesamtscore; Therapieansprechen (anhand HAM-D), Global Impression-Improvement Skala (CGI-I), Verträglichkeit **Ergebnisse:** Allgemein: Es wurden 6 Studien gegenüber Venlafaxin, Sertralin, Fluoxetin, Paroxetin oder Escitalopram identifiziert. Insgesamt wurden für die Wirksamkeitsanalyse 1997 Patienten (1001 unter Agomelatin und 996 Patienten unter SSRI/SNRI getestet). • Es zeigte sich ein stat. signifikanter Unterschied zwischen den HAM-D Gesamtscores mit einer größeren Reduktion unter Agomelatin verglichen mit SSRI/SNRIs (0.86; 95% KI: 0.18–1.53, p=0.013). • Es zeigte sich ebenfalls ein stat. signifikant besseres Therapieansprechen unter Agomelatin (gemessen anhand der HAM-D Skala; p=0.012 und der Global Impression-Improvement Skala; p=0.032). • Agomelatin wies ein besseres Sicherheitsprofil auf, verglichen mit SSRI/SNRIs. Dies betraf das Auftreten von Nebenwirkungen allgemein (nummerisch im Vorteil) und Studienabbrüche aufgrund von Nebenwirkungen (stat. signifikant vorteilig). Fazit der Autoren: *'Agomelatine has favourable efficacy and tolerability versus a range of SSRIs and SNRIs – including agents considered to have superior efficacy – and may deserve benefit–risk analysis as a first-line treatment of major depressive disorder.'* **Anmerkungen der Autoren und FBMed:** • Unterschiedlicher Studiendauer
Singh et al. 2011: Efficacy of agomelatine in major depressive disorder: a meta-analysis and appraisal.	Systematische Literaturrecherche bis 2011 mit Metaanalyse. **Population**: Patienten mit majorer Depression **Vergleich:** Agomelatin vs. andere Antidepressiva (Fluoxetin, Paroxetin, Sertralin, Venlafaxin) **Endpunkte**: Veränderung des Schweregrades der Depression (anhand HAM-D oder MADRS); Studienabbrüche (allgemein und aufgrund von Nebenwirkungen des Arzneimittels) **Ergebnisse** (es lagen 5 direkt vergleichende Studien vor): • Es zeigte sich ein kleiner aber stat. signifikanter Unterschied zwischen

	den Gruppen zum Vorteil von Agomelatin (SMD:-0.13; p=0.02). • Wenn Agomelatin gegenüber Studien mit Venlafaxin getestet wurde, zeigte sich kein stat. signifikanter Unterschied. • Es zeigten sich stat. signifikant weniger Studienabbrüche unter Agomelatin (4%) gegenüber anderen Antidepressiva (9%) (RD: -0.004; p=0.005). Studienabbrüche aufgrund von Nebenwirkungen des Arzneimittels waren vergleichbar. Fazit der Autoren: *'Although there is evidence of the superiority of agomelatin over placebo and selected antidepressants, it is questionable whether the magnitude of effect size is clinically significant and sample characteristics are relevant to the general patient population with major depressive disorder.'*
De Silva et al. 2012: Efficacy and tolerability of venlafaxine versus specific serotonin reuptake inhibitors in treatment of major depressive disorder: a meta-analysis of published studies. *Siehe auch: Bauer et al. 2009*	Systematische Literaturrecherche von Hanuar 1990 bis September 2010 mit Metaanalyse. **Population**: Erwachsene Patienten mit majorer Depression **Vergleich**: Venlafaxin vs. SSRIs **Endpunkte**: Therapieansprechen, Remission, Studienabbrüche (allgemein und aufgrund von Nebenwirkungen) **Ergebnisse** (basierend auf 26 Studien mit insgesamt 5858 Patienten): • Es zeigte sich eine stat. signifikante Überlegenheit von Venlafaxin gegenüber SSRIs hinsichtlich der Remission (OR= 1.13, 95% KI: 1.0–1.28, p =0.05) und dem Therapieansprechen (OR =1.17, 95% KI= 1.03–1.34,p=0.02). • In einer Subgruppenanalyse zeigte sich ein stat. signifikanter Vorteil unter Venlafaxin hinsichtlich der Ansprechrate, wenn verglichen wurde gegen Fluoxetin (OR= 1.28, 95% KI= 1.05–1.55, p = 0.01). • Es zeigten sich keine stat. signifikanten Unterschiede hinsichtlich der Remission und des Therapieansprechens zwischen Venlafaxin und anderen SSRIs. • Studienabbrüche aufgrund jeglicher Ursache waren nicht stat. signifikant unterschiedlich; jedoch zeigten sich stat. signifikant mehr Studienabbrüche aufgrund von Nebenwirkungen, wenn verglichen wurde mit SSRIs (OR: 1.41, 95% KI= 1.10–1.79, p=0.006). Fazit der Autoren: *'The superior efficacy of venlafaxine over SSRIs is of clinical importance. However, higher rates of discontinuation due to adverse events for venlafaxine compared with SSRIs are a disadvantage.'*
Cipriani et al. 2008: Does Randomized Evidence Support Sertraline as First-Line Antidepressant for Adults With Acute Major Depression? A Systematic Review and Meta-Analysis.	Systematische Literaturrecherche bis 2007 mit Metaanalyse. **Population:** Patienten mit majorer Depression **Vergleich:** Sertralin vs. einem anderen Antidepressivum **Endpunkte:** Therapieansprechen, Studienabbrecher nach 8 Wochen aufgrund von jeglicher Ursache **Ergebnisse** (basierend auf 56 RCTs mit insgesamt 8507 Patienten): Wirksamkeit: • Sertralin vs. Trizyklische Antidepressiva: Keine stat. signifikanten Unterschiede; weder gegenüber individueller trizyklischer Antidepressiva oder den trizyklischen Antidepressiva als Klasse. • Sertralin vs. SSRIs*:* Es zeigte sich ein stat. signifikanter Vorteil unter Sertralin gegenüber SSRIs als Klasse (RR: 0.88, 99% KI = 0.78 - 0.99) und gegenüber Fluoxetin (RR: 0.85, 99% KI = 0.74 - 0.98); nicht jedoch gegenüber anderen individuellen SSRIs. • Sertralin vs. andere Antidepressiva: Es wurden keine stat. signifikanten Unterschiede identifiziert.

	Sicherheit: • Es zeigten sich keine stat. signifikanten Unterschiede zwischen Sertralin und den anderen Kontrollgruppen (weder als Klasse noch hinsichtlich individueller Vergleichen). Fazit der Autoren: *'The results of this review suggest that sertraline may be a candidate as the initial choice of antidepressant for people with major depression.'* **Anmerkungen der Autoren und FBMed:** • Teilweise hohe Heterogenität zwischen den Studien (>50%; z.B.: Vergleich von Sertralin vs. Fluvoxamin und Sertralin vs. Paroxetin)
Bauer et al. 2010: A pooled analysis of two randomised, placebo-controlled studies of extended release quetiapine fumarate adjunctive to antidepressant therapy in patients with major depressive disorder.	1. Fragestellung: Evaluation of adjunctive extended release quetiapine fumarate (quetiapine XR) in patients with major depressive disorder (MDD) showing inadequate response to antidepressant treatment.
	2. Methodik Population: Patients with major depressive disorder (MDD) showing inadequate response to antidepressant treatment. Intervention: Once-daily quetiapine XR 150 mg/day (n=309), 300 mg/day (n=307) adjunctive to ongoing antidepressant therapy. Komparator: Placebo (n=303) adjunctive to ongoing antidepressant therapy. Endpunkt: • Primary endpoint: change from randomisation to Week 6 in MADRS total score. • Secondary endpoints: MADRS response (≥50% decrease in total score) and remission (total score≤8), change from randomisation in HAM-D, HAM-A, PSQI global and CGI-S scores, Adverse events (AEs) and withdrawals due to AEs Suchzeitraum: Beide Studien jeweils zwischen 2006/2007 durchgeführt Anzahl eingeschlossene Studien/Patienten (Gesamt): 2 Studien mit insgesamt 919 Patienten.
	3. Ergebnisdarstellung Note: *Subgroup analyses of the primary variable were made by severity of depression, age and gender* Primary endpoint: • Quetiapine XR (150 and 300 mg/day) reduced MADRS total scores vs placebo at every assessment including Week 6 (−14.5, −14.8, −12.0; p<0.001 each dose) and Week 1 (−7.8, −7.3, −5.1; p<0.001 each dose). Response: • MADRS response (≥50% decrease in total score) rates at Week 1 were 18.6% (p<0.01, compared with placebo), 17.5% (p<0.05, compared with placebo) and 10.8% for quetiapine XR 150 mg/day, quetiapine XR 300 mg/day and placebo, respectively. At Week 6, response rates were 53.7% (p=0.063), 58.3% (p<0.01) and 46.2%, respectively. Remission: • Remission (MADRS total score ≤8) rates at Week 6 were 35.6% (pb0.01) and 36.5% (pb0.001) in the quetiapine XR 150 mg/day and 300 mg/day groups, respectively vs placebo (24.1%) Using more common definitions of remission (MADRS total score ≤10 and ≤12), higher rates of remission were observed at Week 6 in the quetiapine XR 150 mg/day and 300 mg/day groups compared with placebo (≤10: 41.8%, 46.3% and 32.0%, respectively; ≤12: 49.8%, 53.1% and 40.3%, respectively).

	Other secondary endpoints: • Significant improvements in HAM-D and HAM-A total scores, CGI-S score and PSQI global score were seen at Week 6 with quetiapine XR 150 mg and 300 mg, compared with placebo. However, no significant improvement was seen in Q-LES-Q % maximum total score with either dose of quetiapine XR at Week 6, compared with placebo. AEs: • AEs were experienced by 73.3%, 80.8% and 60.2% of patients in the quetiapine XR 150 mg/day, 300 mg/day and placebo groups, respectively. • Most AEs were mild to moderate in severity. SAEs were reported by 1.0%, 1.0% and 1.3% of patients in the quetiapine XR 150 mg/day, 300 mg/day and placebo groups, respectively. • The percentage of patients who withdrew from the studies due to AEs was higher in quetiapine XR-treated patients (150 mg/day, 8.9%; 300 mg/day, 15.4%), compared with placebo (1.9%). In the quetiapine XR groups, the most common AEs leading to withdrawal were somnolence (150 mg/day, 2.9%; 300 mg/day, 3.2%) and sedation (150 mg/day, 1.9%; 300 mg/day, 4.8%). Subgruppenanalysen: • Analysis of the change in mean MADRS total scores from randomisation at Week 6 by class of adjunctive antidepressant showed significantly greater improvementswith quetiapine XR 150 and 300 mg/day, compared with placebo as adjunct to SSRIs (−14.8,−14.7 and−12.7, respectively; p<0.05, for each dose) and SNRIs (−14.8, −15.1 and −10.8, respectively; p<0.01, for each dose). • Analysis of the primary endpoint using MADRS Item 4 (reduced sleep) score as a covariate showed that treatment with quetiapine XR 150 mg/day and 300mg/day led to significant improvements from randomisation in MADRS total score at Week 6 (−14.6 [p<0.001] and−15.0 [p<0.001], respectively) compared with placebo (−12.1). • An additional analysis of patients with and without somnolence (as determined by an AE associated with a sedative effect) was undertaken. It should be noted that as these patients represent subpopulations they were not inherently randomised. At Week 6, quetiapine XR (dose groups combined) significantly improved MADRS total score in patients reporting sedation/somnolence (n=250), compared with placebo (n=303) (−14.9 and −12.0, respectively; p<0.001). In patients not reporting sedation/somnolence (n=366) mean change in MADRS score was also significantly improved, compared with placebo (−14.4 and −12.0, respectively; p<0.001).
	4. Fazit der Autoren: *Adjunctive quetiapine XR is effective in patients with MDD and an inadequate response to antidepressant therapy, with improvement in depressive symptoms seen as early as Week 1.*
Santaguida (AHRQ), 2012: Treatment for Depression After Unsatisfactory Response to SSRIs	1. Fragestellung: First question: Among adults and adolescents with major depressive disorder, dysthymia, and subsyndromal depression, who are started on an SSRI and who are compliant with treatment but fail to improve either fully, partially, or have no response, what is the benefit (efficacy or effectiveness) of monotherapy and combined therapy? Second question: What are the harms of each of the monotherapies or combined therapies among these adults and adolescents? How do the harms compare across different interventions?
	2. Methodik Population: Adults (aged ≥18 years) or adolescents and children (8–18 years) with major depressive disorder, dysthymia, or subsyndromal depression, who had an inadequate response to an SSRI at entry into the study.

	Intervention: • **SSRIs:** Fluoxetine, Citalopram, Fluvoxamine, Sertraline, Paroxetine, Escitalopram • **Non SSRIs:** Duloxetine Hydrochloride, Venlafaxine, Desvenlafaxine Succinate, Phenelzine Sulfate, Tranylcypromine Sulfate, Emsam, Moclobemide, Doxepin, Clomipramine, Amitriptyline, Maprotiline, Desipramine, Trimipramine, Imipramine, Protriptyline Hydrochloride, Agomelatine, Reboxetine, Norvale, Trazodone • **Non-pharmacological and complementary and alternative medicine (CAM) therapies:** cognitive behavioral therapy (CBT), interpersonal therapy (IPT), and other psychotherapies (behavior therapy, counseling, problem-solving therapy, psychodynamic therapy, bibliotherapy, guided self-help, distraction therapy), light therapy, exercise (any type cardiovascular or strengthening or stretching and including yoga, hydrotherapy), CAM including whole body systems (e.g., acupuncture), mind-body medicine (e.g., meditation), manipulative and bodybased practices (e.g., massage), energy medicine (e.g., reiki), biologically based practices (dietary supplements and herbal products: e.g., amino acids, vitamins and minerals, Inositol, herbs, methyl-folate, omega-3 fatty acids, SAMe). • **Augmenters (no formal indication for use as an antidepressant):** Buspirone, Gepirone, Tandospirone, Atypical Antipsychotics (Risperidone, Olanzapine, Quetiapine, Aripiprazole, Ziprasidone), Psychostimulants (Amphetamine, Methylphenidate, Dopamine agonists (Bromocriptine, Cabergoline, Pergolide, Pramipexole, Ropinirole, Apomorphine, Rotigotine, Other drugs (Lithium, Pindolol, Tryptophan), Anticonvulsants (Carbamazepine, Sodium Valproate, Lamotrigine), Antiprogestational agents (Mifepristone), Sex Hormones (Androgens, Estrogens, Progesterone), Thyroid medications (triiodothyronine, Amisulpride, Phenytoin), Modafinil, N-methyl-D aspartate. • Studies that used electroconvulsive therapy, vagal nerve stimulation, or repetitive transcranial nerve stimulation as the intervention were excluded. Komparator: The interventions (either alone or in combination) may be compared with any of the following: 1. Placebo 2. Same SSRI dose but different MDD population (for example, mild vs. severe MDD) 3. Same SSRI of different dose or duration 4. Other SSRI 5. Other antidepressant (from a different drug class) 6. Nonpharmacological or CAM therapies as described above 7. Adjunct therapy: combination of an augmenter plus SSRI 8. Adjunct therapy: combination of nonpharmacological or CAM therapy plus SSRI 9. Adjunct therapy: combination of augmenter and nonpharmacological or CAM therapy Endpunkt: <u>Primary outcomes include the following:</u> 1. Adequate Response: response to treatment is defined as a minimum of 50 percent change relative to baseline using a standardized instrument.3,62 2. Remission: remission is defined as being free or nearly free of symptoms. It is typically established by achieving a threshold score using a standardized instrument.

	3. Partial and Nonresponse: partial response refers to a change in baseline score from 25 to 49 percent. Nonresponse is defined as less than 25 percent change relative to baseline. 4. Speed of Response. 5. Relapse: relapse is defined as a return of symptoms satisfying the full syndrome criteria for an episode which occurs following a period of remission but before recovery. Relapse is the point at which recurrent symptoms are severe enough that the clinician determines an intervention is warranted. Relapse is related but distinct from the term recurrence. Recurrence is defined as the return of the disease after its apparent cessation (symptoms return after a period of remission). <u>Secondary outcomes include the following:</u> • 1. Quality of life • 2. Adherence • 3. Return to work • 4. Global change as measured by global assessment scales • 5. External service utilization Suchzeitraum: 1980 to April 2011 Anzahl eingeschlossene Studien/Patienten (Gesamt): 44 studies and 27 guidelines were eligible.
	3. Ergebnisdarstellung **First Question:** Among adults and adolescents with major depressive disorder, dysthymia, and subsyndromal depression, who are started on an SSRI and who are compliant with treatment but fail to improve either fully, partially, or have no response, what is the benefit (efficacy or effectiveness) of monotherapy and combined therapy?: • Forty-one studies included adults and three studies included adolescents; all included subjects with major depressive disorder except for one with adult dysthymia and subsyndromal patients alone. **<u>Monotherapy Versus Monotherapies in Adults:</u>** Twelve studies (n=2,611) compared monotherapy interventions relative to other monotherapies. The interventions were a minimum of 4 weeks duration and three of the studies involved dose escalation of sertraline, venlaxafine, or paroxetine. The remaining eight studies evaluated head-to-head comparison following switching from: (1) citalopram to venlaxafine, bupropion, sertraline, or cognitive behavior therapy (CBT); (2) paroxetine to venlaxafine; (3) fluoxetine to olanzapine or mianserin; or, (4) from an SSRI to duloxetine (tapering methods). • The findings suggest that there is no certainty of any advantage between different monotherapies (pharmacological or nonpharmacological) for either response to treatment or remission. The exception was a single study that showed that lower-dose sertraline had some small improvement in response, and that the frequency of adverse events decreased at the higher dose; this particular study also suggests that the differences may have been related to the longer trial duration as subjects were randomized after failure to respond to the lower dose. There is limited evidence to establish with certainty that a dose escalation or a switch to another antidepressant (SSRI or non-SSRI) is equivalent or superior to any comparator treatment in patients with inadequate response to an initial SSRI; our limited pool of studies would suggest that these monotherapies are equivalent in their treatment effects. **<u>Monotherapies Versus Combined Treatment in Adults:</u>** Total of 33 studies (49 publications) evaluated the efficacy and effectiveness of monotherapy relative to combined therapies. All but one study employed a randomized controlled trial (RCT) design, and all studies included a pharmacological intervention for at least one treatment arm. The

	majority of studies employed a study design that had the comparator arm receive ongoing treatment with an SSRI to which the subjects had not had an adequate response by the start of the study; fewer studies employed a design in which patients were switched to a new treatment in at least one study arm. Four studies had one treatment arm that evaluated a combination therapy that included the non-SSRI antidepressants clomipramine, bupropion, or desipramine. Twenty-six of 33 studies evaluated combination therapies that included augmenting agents. From these, only five augmenting agents were evaluated in two or more studies; these included atypical antipsychotics (olanzapine and risperidone), lithium, buspirone, mianserin, and pindolol. Five studies evaluated the use of nonpharmacological interventions including CBT, dialectical behavior therapy, interpersonal therapy, and exercise. • The majority of studies showed no certainty of any difference for any monotherapy treatment, relative to the comparator combined therapy, for the outcomes of response and remission. The exception was with the atypical antipsychotics (olanzapine, risperidone, ariprazole, quetiapine) used as augmenting agents, which showed small differences favoring the combination therapy. Overall, there is limited supportive evidence for any single augmenting drug or for switching to a different antidepressant (monotherapy) relative to adding another treatment (pharmacological or nonpharmacological). **<u>Combined Therapies Versus Combined Therapies in Adults:</u>** There were six studies (n=832) for which there were treatment arms that compared combination therapies with each other. All but one study were RCTs. In addition to SSRIs, added therapies included lithium, desipramine, buspirone, bupropion, citalopram, clomipramine, or CBT. • There was no certainty of a difference between any combination therapy, including a dose escalation, for the added augmenting agent. **<u>Second question:</u>** What are the harms of each of the monotherapies or combined therapies among these adults and adolescents? How do the harms compare across different interventions?: • Harms for interventions used for both adults and adolescents with MDD who had failed to respond to an SSRI were predominately derived from RCTs that evaluated treatment strategies in this population. No observational studies met the eligibility criteria. A clear trend for harms was difficult to specify across the differing interventions in adults. In general, the majority of harms reported were consistent with those associated with antidepressant use and were likely mild to moderate in nature.
	4. <u>Fazit der Autoren:</u> *There is low strength of evidence evaluating relative differences for any monotherapy or combination therapy approach. All but 2 of 44 studies showed no relative differences in response and remission rates. Two studies with limited sample sizes and using risperidone as an augmenting agent showed benefit with combined therapy. The majority of studies were not designed to assess superiority of the strategies. Inconsistency and lack of clarity for clinical actions were noted when comparing CPGs.*
Papakostas et al. 2008: Treatment of SSRI-Resistant Depression: A Meta-Analysis Comparing Within- Versus Across-Class Switches	1. Fragestellung: Meta-analysis of studies comparing two switch strategies.
	2. Methodik Population: Patients with SSRI-resistant Depression Intervention: Switching to an SSRI (Sertraline, one citalopram, and one Paroxetine) vs. a non-SSRI (three venlafaxine, one mirtazapine, one bupropion) antidepressant Endpunkt:

	• Primary endpoint: Remission rates • Secondary endpoints: Response rates, rate of discontinuation due to intolerance Suchzeitraum: Six search strategies were employed to help identify studies for inclusion in the meta-analysis. Kein Suchzeitraum angegeben. Anzahl eingeschlossene Studien/Patienten (Gesamt): 4 studies (N=1496 patients)
	3. Ergebnisdarstellung • Patients randomized to switch to a non-SSRI antidepressant (bupropion, mirtazapine, venlafaxine) were more likely to experience remission than patients who were switched to a second SSRI (citalopram, paroxetine, sertraline). The pooled risk ratio for remission was 1.29 (95% confidence interval [CI]: 1.07–1.56; p=0.007). • There was no difference in response rates between the two treatment groups (RR: 1.059, 95% CI: 0.9 –1.23, p=0.49). • There was a non-significant trend in the rates of discontinuation due to intolerance favoring the within-class switch strategy (RR: 1.23, 95% CI: 0.95–1.59; p=0.101). The rate of discontinuation due to intolerance was 17.7% for the non-SSRI agents and 11.5% for the SSRIs. • Because three of the five comparisons utilized venlafaxine as the non-SSRI, the meta-analysis was repeated examining only those three studies. Patients switched to venlafaxine were more likely to experience remission than patients switched to an SSRI (p=0.03). The RR for remission was 1.31 (95% CI: 1.02–1.67). There was no difference in the rate of discontinuation due to intolerance between the two treatment groups (RR: 1.03; 95% CI .71–1.50; p=0.85).
	4. Fazit der Autoren: *These results suggest a modest yet statistically significant advantage in remission rates when switching patients with SSRI-resistant depression to a non-SSRI rather than an SSRI antidepressant. With the number needed to treat (NNT) statistic as one indicator of clinical significance, nearly 22 SSRI non responders would need to be switched to a non-SSRI rather than a second SSRI antidepressant to obtain one additional remitter. This difference falls well below the mark of NNT 10 suggested by the United Kingdom's National Institute of Clinical Excellence but nonetheless might be of public health relevance given the large number of SSRI-resistant patients switched to an SSRI versus a non-SSRI antidepressant.*
Gaynes (AHRQ), 2011: Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults.	1. Fragestellung: Comparison of the efficacy, effectiveness, and harms of nonpharmacologic interventions for TRD in adults. Research questions addressed: • 1a: For adults with treatment-resistant depression (TRD, defined as two or more failed adequate trials of a biologic intervention), do nonpharmacologic interventions such as electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), or demonstrated effective psychotherapy (e.g., cognitive therapy [CBT or IPT]) differ in efficacy or effectiveness in treating acute-phase depressive symptoms (e.g., response and remission), whether as a single treatment or part of a combination treatment? • 1b: How do these nonpharmacologic treatments compare with pharmacological treatments in efficacy or effectiveness in treating acute-phase depressive symptoms after two or more failed adequate trials? • 2: For adults with TRD, do nonpharmacologic interventions differ in their efficacy or effectiveness for maintaining response or remission (e.g., preventing relapse or recurrence), whether as a single treatment or part of a combination treatment? • 3. Do nonpharmacologic interventions (single or combination) differ in their efficacy or effectiveness for treating TRD as a function of particular

	symptom subtypes (e.g., catatonic [frozen or hyper] or psychotic symptoms)? • 4a: For adults with TRD, do nonpharmacologic interventions differ in cognitive functioning? • 4b: For adults with TRD, do nonpharmacologic interventions differ in specific adverse events? • 4c: For adults with TRD, do nonpharmacologic interventions differ in withdrawals due to adverse events? • 4d: For adults with TRD, do nonpharmacologic interventions differ in adherence (as measured by overall withdrawal) • 5: For adults with TRD, do nonpharmacologic interventions differ in harms for selected populations? • 6: For adults with TRD, do nonpharmacologic interventions differ in regard to other health-related outcomes (e.g., quality of life)?
	2. Methodik Population: Adults with treatment-resistant depression (TRD), defined as two or more failed adequate trials of a biologic intervention. Intervention/Komparator: Nonpharmacologic somatic treatments and nonsomatic psychotherapy treatments (ECT, rTMS, VNS, and psychotherapy (e.g., cognitive therapy, such as cognitive behavioral therapy [CBT or IPT]). Or nonpharmacologic treatments vs. pharmacological treatments Endpunkt: changes in depressive severity, rates of response, and rates of remission, health-related outcomes (QoL), Adverse events Suchzeitraum: 1980 to November 2010 Anzahl eingeschlossene Studien/Patienten (Gesamt): 79 good-, fair-, or poorquality that represent 64 studies. Of these studies, there were 17 head-tohead RCTs (19 articles): 7 studies (9 articles) were head-to-head RCTs of a nonpharmacologic intervention versus a nonpharmacologic intervention; 3 were head-to-head RCTS of a nonpharmacologic intervention versus a pharmacologic one; and 7 were head-to-head studies of a pharmacologic versus pharmacologic intervention. Further, there were 38 additional RCTs (50 articles) that were sham- or placebo-controlled, and 2 observational studies (2 articles). The review presents evidence that allows comparison of the four nonpharmacologic treatments of interest (ECT, rTMS, VNS, and psychotherapy).
	3. Ergebnisdarstellung 1a: For adults with TRD, do nonpharmacologic interventions differ in efficacy or effectiveness in treating acute-phase depressive symptoms (e.g., response and remission), whether as a single treatment or part of a combination treatment?

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
ECT vs. rTMS	Change in depressive severity	42	Low	1 fair trial: both ECT and rTMS improved severity but did not differ significantly.
ECT vs. rTMS	Response rate	42	Low	1 fair trial: ECT and rTMS did not differ sig
ECT vs. rTMS	Remission rate	42	Low	1 fair trial: ECT and rTMS did not differ sig
ECT plus rTMS vs. ECT	Change in depressive severity	22	Low	1 fair trial: both ECT and ECT plus rTMS symptom severity but did not differ signific
ECT plus rTMS vs. ECT	Response rate	0	NA	No eligible studies identified.‡
ECT plus rTMS vs. ECT	Remission rate	22	Low	1 fair trial: ECT and ECT plus rTMS did n significantly.
ECT vs. sham	Change in depressive severity	0	NA	No eligible studies identified.‡
ECT vs. sham	Response rate	0	NA	No eligible studies identified.‡
ECT vs. sham	Remission rate	0	NA	No eligible studies identified.‡
rTMS vs. sham	Change in depressive severity	497	High	7 trials (3 good, 4 fair): rTMS had a signifi greater decrease in depressive severity th 4 fair trials: rTMS had nonsignificantly gre decrease in depressive severity than sha 2 fair trials: rTMS had greater decrease th but significance NR. 1 fair trial: rTMS did not significantly differ sham.
rTMS vs. sham	Response rate	471	High	4 trials (3 good, 1 fair): rTMS had a signifi higher response rate than sham. 1 fair trial: rTMS had a nonsignificantly hig response rate than sham. 6 fair trials: rTMS had a higher response sham, but significance NR. 1 fair trial: rTMS did not clearly differ from significance NR.
rTMS vs. sham	Remission rate	223	Moderate	3 trials (2 good, 1 fair): rTMS had significa greater remission rate than sham. 1 fair trial: rTMS had a greater remission sham but significance NR.
VNS vs. sham	Change in depressive severity	235	Low	1 good trial: VNS and sham did not differ significantly.
VNS vs. sham	Response rate	235	Low	1 good trial: VNS and sham did not differ significantly.
Psychotherapy vs. control	Change in depressive severity	0	NA	No eligible studies identified.‡
Psychotherapy vs. control	Response rate	0	NA	No eligible studies identified.‡
Psychotherapy vs. control	Remission rate	0	NA	No eligible studies identified.‡

ECT = electroconvulsive therapy; NA = not applicable; NR = not reported; rTMS = repetitive transcranial magnetic stimu
VNS = vagus nerve stimulation; vs. = versus

*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Review text.

†Good and fair designations relate to quality ratings for each study.

‡At least one Tier 2 or Tier 3 study addressed this comparison.

1b: How do these nonpharmacologic treatments compare with pharmacological treatments (only 1 study with paroxetine) in efficacy or effectiveness in treating acute-phase depressive symptoms after two or more failed adequate trials?

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
ECT vs. pharmacotherapy	Change in depressive severity	39	Low	1 fair trial: ECT had significantly greater improvement in symptom severity than pharmacotherapy.
ECT vs. pharmacotherapy	Response rate	39	Low	1 fair trial: ECT had significantly greater rates than pharmacotherapy.
Psychotherapy vs. pharmacotherapy	Change in depressive severity	0	NA	No eligible studies identified. ‡
Psychotherapy vs. pharmacotherapy	Response rate	0	NA	No eligible studies identified. ‡
Psychotherapy vs. pharmacotherapy	Remission rate	0	NA	No eligible studies identified. ‡

ECT = electroconvulsive therapy; NA = not applicable; rTMS = repetitive transcranial magnetic stimulation; vs. = versu
*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Revie
text.
†Good and fair designations relate to quality ratings for each study.
‡At least one Tier 2 and/or Tier 3 study addressed this comparison.

2: For adults with TRD, do nonpharmacologic interventions differ in their efficacy or effectiveness for maintaining response or remission (e.g., preventing relapse or recurrence), whether as a single treatment or part of a combination treatment?

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
ECT vs. rTMS	Maintenance of remission	0	NA	No eligible studies identified. ‡
rTMS vs. sham	Maintenance of remission	68	Insufficient	3 fair trials: no significant differences i maintenance of remission; however, s sizes in two of the studies and the pres co-intervention in the third study make difficult to interpret.
CBT vs. usual care	Maintenance of remission	0	NA	No eligible studies identified. ‡

CBT = cognitive behavioral therapy; ECT = electroconvulsive therapy; NA = not applicable; rTMS = repetitive transcra
magnetic stimulation; vs = versus
*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Revie
text.
†Good and fair designations relate to quality ratings for each study.
‡At least one Tier 2 and/or Tier 3 study addressed this comparison.

3. Do nonpharmacologic interventions (single or combination) differ in their efficacy or effectiveness for treating TRD as a function of particular symptom subtypes (e.g., catatonic [frozen or hyper] or psychotic symptoms)?

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
ECT vs. rTMS	Change in depressive severity	0	NA	No eligible studies identified.

ECT = electroconvulsive therapy; NA = not applicable; rTMS = repetitive transcranial magnetic stimulation; vs. = versu
*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Revie
text.
†Good and fair designations relate to quality ratings for each study.
‡At least one Tier 2 and/or Tier 3 study addressed this comparison.

4a: For adults with TRD, do nonpharmacologic interventions differ in cognitive functioning?

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
ECT vs. rTMS	Cognitive functioning	72	Insufficient	1 fair trial and 1 fair cohort study: Some suggests no difference between treatm whereas some evidence suggests ECT deleterious impact on cognitive function compared with rTMS (1 study: significa 1-week recall; both studies: nonsignifica all other measures).
ECT vs. ECT + rTMS	Cognitive functioning	22	Insufficient	1 fair trial: no significant differences in a measure on memory problems.
rTMS vs. sham	Cognitive functioning	161	Insufficient	4 trials (1 good, 3 fair): Some evidence no difference between rTMS and sham, some evidence suggests that rTMS imp cognitive functioning compared to sham (2 trials: significant differences in mem fluency; all other findings nonsignificant significance not reported).

ECT = electroconvulsive therapy; rTMS = repetitive transcranial magnetic stimulation; vs. = versus
*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Revie text.
†Good and fair designations relate to quality ratings for each study.

4b: For adults with TRD, do nonpharmacologic interventions differ in specific adverse events?

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
ECT vs. rTMS	Adverse events	0	NA	No eligible studies identified.‡
ECT vs. ECT + rTMS	Adverse events	22	Low	1 fair trial: no significant differences in s adverse events
rTMS vs. sham	Adverse events	68	Low	1 good trial: rTMS resulted in significant scalp pain at the stimulation site than sl
VNS vs. sham	Adverse events	235	Low	1 fair trial: Some differences in specific events reported (*P* = NR)

ECT = electroconvulsive therapy; NA = not applicable; rTMS = repetitive transcranial magnetic stimulation; VNS = va stimulation; vs. = versus
*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Revie text.
†Good and fair designations relate to quality ratings for each study.
‡At least one Tier 2 and/or Tier 3 study addressed this comparison.

4c: For adults with TRD, do nonpharmacologic interventions differ in withdrawals due to adverse events?

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
ECT vs. rTMS	Withdrawals	30	Low	1 fair cohort study: no difference in with between ECT and rTMS groups (*P* = NI
ECT vs. sham	Withdrawals	0	NA	No eligible studies identified.‡
rTMS vs. sham	Withdrawals	337	Insufficient	7 trials (1 good, 6 fair): trials showed mi about withdrawals attributed to adverse
VNS vs. sham	Withdrawals	235	Low	1 good trial: VNS had greater withdrawa attributed to adverse events than sham (significance NR).
CBT vs. usual care	Withdrawals	0	NA	No eligible studies identified.‡

CBT = cognitive behavioral therapy; ECT = electroconvulsive therapy; NA = not applicable; NR = not reported; rTMS repetitive transcranial magnetic stimulation; VNS = vagus nerve stimulation; vs. = versus
*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Revie text.
†Good and fair designations relate to quality ratings for each study.
‡At least one Tier 2 and/or Tier 3 study addressed this comparison.

4d: For adults with TRD, do nonpharmacologic interventions differ in adherence (as measured by overall withdrawal)?

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
ECT vs. rTMS	Overall withdrawals	72	Low	1 fair trial and 1 fair cohort study: studie more withdrawals in the ECT group com rTMS (*P* = NR).
ECT vs. sham	Overall withdrawals	0	NA	No eligible studies identified. ‡
rTMS vs. sham	Overall withdrawals	325	Insufficient	8 fair trials: trials showed mixed results withdrawals.
CBT vs. usual care	Overall withdrawals	0	NA	No eligible studies identified. ‡

CBT = cognitive behavioral therapy; ECT = electroconvulsive therapy; NA = not applicable; rTMS = repetitive transcra magnetic stimulation; vs. = versus
*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Revie text.
†Good and fair designations relate to quality ratings for each study.
‡At least one Tier 2 and/or Tier 3 study addressed this comparison.

5: For adults with TRD, do nonpharmacologic interventions differ in harms for selected populations?

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
rTMS vs. sham	Changes in depressive severity	34	Low	1 fair trial: rTMS produced better outcom sham in young adult population (ages 1
rTMS vs. sham	Changes in depressive severity	20	Low	1 fair trial: rTMS produced better outcom sham in older adults with post-stroke de
rTMS vs. sham	Response	34	Low	1 fair trial: rTMS produces better respon than sham in young adult population (ag
rTMS vs. sham	Response	20	Low	1 fair trial: no difference between rTMS for older adults with post-stroke depress
rTMS vs. sham	Remission	20	Low	1 fair trial: no difference between rTMS in older adults with post-stroke depressi

rTMS = repetitive transcranial magnetic stimulation; vs. = versus
*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Revie text.
†Good and fair designations relate to quality ratings for each study.

6: For adults with TRD, do nonpharmacologic interventions differ in regard to other health-related outcomes (e.g., quality of life)?

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
ECT vs. ECT + rTMS	Health-related outcomes	22	Low	1 fair trial: There were no differences between gr improvements in daily functioning.
rTMS vs. sham	Health-related outcomes	60	Low	1 fair trail: low rTMS had significantly greater imp in health status and daily functioning than sham, relationship approached statistical significance w comparing high rTMS to sham.
VNS vs. sham	Health-related outcomes	214	Low	1 fair trial: VNS and sham groups did not differ si in daily functioning.
CBT/DBT vs. control	Health-related outcomes	0	NA	No eligible studies identified. ‡

CBT = cognitive behavioral therapy; DBT = dialectical behavioral therapy; NA = not applicable; rTMS = repetitive tr magnetic stimulation; VNS = vagus nerve stimulation; vs. = versus
*Strength of evidence is based on the on guidance provided in the AHRQ Methods Guide for Comparative Effectiven Reviews; see text.
†Good and fair designations relate to quality ratings for each study.
‡At least one Tier 2 and/or Tier 3 study addressed this comparison.

4. Fazit der Autoren: *Our review suggests that comparative clinical research on nonpharmacologic interventions in a TRD population is in its infancy, and many clinical questions about efficacy and effectiveness remain unanswered. Interpretation of the data is substantially hindered by varying definitions of TRD and the paucity of relevant studies. The greatest volume of evidence is for ECT and rTMS; however, even for the few comparisons of treatments that are supported by some evidence, the strength of evidence is low for comparative benefits. Specifically, there was low strength of evidence that ECT and rTMS did*

	not produce different clinical outcomes in TRD, and low strength of evidence that ECT produced better outcomes than pharmacotherapy. No trials directly compared the likelihood of maintaining remission for nonpharmacologic interventions. The few trials addressing adverse events, subpopulations, subtypes, and health-related outcomes provided low or insufficient evidence of differences between nonpharmacologic interventions. The most urgent next steps for research are to apply a consistent definition of TRD, to conduct more head-to-head clinical trials comparing nonpharmacologic interventions to one another and to pharmacologic treatments, and to carefully delineate the number of adequate treatment failures in the current episode.
Ruhe et al. 2006 (per Handsuche): Switching Antidepressants after a first selective serotonin reuptake inhibitor in major depressive disorder: a systematic review.	1. Fragestellung: To systematically review the evidence for switching pharmacotherapy after a first SSRI.
	2. Methodik **Population:** Patients with major depressive disorder with insufficient response to SSRIs. (*Note*: at least 50% of participants used SSRIs previously in the current depressive disorder.) Intervention/Komparator: Different switsching strategies (e.g. second SSRI, TCAs, novel-dual-acting agents, agents affecting dopaminergic and/or noradrenergic neurotransmission) Endpunkt: Response rates, remission rates, drop out rates due to side effects Suchzeitraum: bis Februar 2005 Anzahl eingeschlossene Studien/Patienten (Gesamt): 31 studies.
	3. Ergebnisdarstellung: Second SSRI (based on 7 open studies): • Response rates of switching in SSRI nonresponders varied between 46% and 58% in 3 uncontrolled studies of variable methodological quality. The response rate was lower (42%) in a fourth study with a heterogeneous group of inpatients. However, response rates to a second SSRI varied between 56% and 72% when patients were intolerant to the first SSRI (4 studies). • Dropout rates due to side effects were between 5% and 21% in studies with initial nonrepsonders and between 0% and 10 % in SSRI-intolerant samples (LoE: C). • In the SSRI arms or 3 RCTs, response rates varied between 26.7% and 71.1%, while remission rates were between 17.6% and 52.1%. • Dropout rates due to side effects varied between 4.8% and 21%. (LoE: A2-B). • In summary, the data from the open studies and 1 of the RCTs suggest, that after 1 SSRI, nonresponders and, notably, also SSRI intolerant patients can benefit from a switch to a second SSRI with response rates of approximately 50% and 70%, respectively. However, the results in 2 RCTs indicated much less advantageous response and remission rates for a second SSRI (26.7%-29% and 17.6%, respectively). TCAs and Mianserin (2 RCTs and 4 open studies with a switch to a TCA were identified): • For the switch to a TCA, response rates of approximately 16.5% to 48.5% were found. Lower response rates were observed in studies that included more treatment-resistant patients. Mirtazapine, Nefazodone, or Venlafaxine (novel dual-acting agents) (13

	studies identified; four studies were RCTs (methodological quality varied): • In the open studies, mirtazapine, nefazodone, and venlafaxine showed response rates between 17% and 86%, with decreased response rates at increased levels of treatment resistance (LoE: C). • Dropout rates due to adverse effects varied between 5.5% and 11% for venlafaxine and between 20.8% and 25.7% for mirtazapine and the rate was 38.5% in 1 study with nefazodone (LoE: A2, C). • A meta-analysis of the 3 RCTs that compared switching to venlafaxine versus SSRIs was performed, although the differences in duration of follow-up introduced some heterogeneity. The weighted difference in remission rates was 8% (4-11%) in favor of venlafaxine and for response was 6% (1-10%). • Omission of the methodological poorer study of a study by Baldomero et al. increased the difference in remission rates (10%; 95%KI: 3-16%), but decreased the difference in response rates (4%; 95%KI: -3;12%). The dropout rate due to side effects was only reported in 2 Studies (WD: 1%; 95%KI. -5;7%), with more dropout for venlafaxine. • In summary, heterogeneous studies considering switching to mirtazapine, nefazodone, and venlafaxine showed response rates of approx. 28%-50% in subjects without obvious TRD, while in subjects with increased levels of TRD, response percentages dropped (investigated for venlafaxine and mirtazapine). Pooling of results showed a modest and clinically equivocally advantageous increased remission rate for venlafaxine over SSRIs. Bupropion and Reboxetine (agents especially affecting dopaminergic and(or noradrenergic neurotransmission) (1 RCT and 2 small open studies were identified): • Switching form Fluoxetine was investigated, with reported response rates of 34,6% for bupropion and 45.3% for reboxetine. For bubpropion, specified dropout rates were not reported in 1 study. The side effect-related dropout rate was 10.3% in subjects with sexual dysfunction while taking fluoxetine. For reboxetine, the dropout rate due to side effects was 13.3% (LoE: C). • In summary, switching to bupropion or reboxetine was scarcely studies but was a possible option with response rates of 26-1% to 34.6% and 45.4%, respectively. The remission rate of switching to bupropion was not different compared with venlafaxine or sertraline. Reversible inhibitor of monoamine-oxidase A: • No studies identified Monoamine-oxidase A inhibitor (2 RCTs and 1 unblinded, randomized, crossover study identified): • One study found, tranylcypromine to be more efficacious than nomifensine; in their studies, the response rates for tranylcypromine were 42,9% and 45.5%. All patients previously received at least fluvoxamine and oxaprotiline. Fifty-eight percent to 62% had side effects affecting their blood pressure levels (LoE: B). • The Star*D level IV study included patients who had not been in remission after citalopram treatment (level: I); who received venlafaxine, bupropion, sertraline, or citalopram augmentation with buspirone or bupropion (level: II); and who additionally received nortriptyline or mirtazapine (level: III). These patients were randomized between trancylpromine and a combination of venlafaxine with mirtazapine. Of the included patients, 32.1% were intolerant of the level III medication. Remission rates were low for tranylcypromine (6.9%) and the combination treatment (13.7%). Response rates were also not significantly different: 12.1% vs. 23.5% for tranylcypromine and

	venlafaxine with mirtazapine, respectively. Dropout rates due to side effects were higher for tranylcypromine: 41.4% vs. 21.6% for venlafaxine with mirtazapine.
	4. Fazit der Autoren*: After a first SSRI, any switch within or between classes of antidepressants appears legitimate (second SSRI, novel-dual-acting antidepressants, selective norepinephrine or noradrenergic/dopaminergic agents, or tricyclic antidepressant or mianserin). No unequivocal evidence is available to prove an advantage of a between-class switch. More guidance by randomized empirical studies is needed. Clinical implications and methodological considerations for future studies are discussed.*
	5. Hinweise: • Well-designed switch studies are scarce (predominately open, uncontrolled studies) • Only few studies that clearly described the inclusion of prospectively determined SSRI nonresponders (risk of recall bias when retrospectively determined). • Small sample sizes (N<40)
Crossley et al. 2007 (per Handsuche): Accerleration and Augmentation of antidepressants with lithium for depressive disorders: two meta-analyses of randomized, placebo-controlled trials.	1. Fragestellung**:** Determine the efficacy of lithium in acceleratin and in augmenting clinical response in patients with depression.
	2. Methodik Population: Subjects with unipolar or bipolar disorder. Intervention: Antidepressant plus lithium Komparator: Antidepressant plus placebo Endpunkt: changes in depression scales‘ ratings at 1 to 2 weeks after treatment, number of patients responding to treatment Suchzeitraum: 1966-2006 Anzahl eingeschlossene Studien/Patienten (Gesamt): 10 studies
	3. Ergebnisdarstellung *Note: For accelerating meta-analysis, studies had to include only subjects without previous appropriate treatment for the depressive episode. For the augmentation meta-analysis, studies had to include patients not responding to conventional antidepressants.* **Lithium Acceleration Meta-Analysis:** • 5 studies considered for analysis. • Normalized depressive scores: No difference between Lithium and the control arm (SMD: -0.43; 95%KI: -0.93; 0.07; p=0.09; I^2=53%). **Lithium Augmentation Meta-Analysis:** • 10 studies considered for analysis. • There was a stat. significant effect in favor of lithium versus placebo (OR: 3.11; 95%KI: 1.80-5.37; p<0.0001; I^2=24.4%)
	4. Fazit der Autoren: *There is firm evidence for lithium as an effective augmentation strategy but only modest evidence for lithium to accerlerate response to antidepressants in patients with depressive disorder.*
	5. Hinweis: • Auch Patienten mit einer bipolaren Störung berücksichtigt.
Trivedi et al. 2010: Examination of the Utility of Psychotherapy for Patients with Treatment Resistant Depression: A Systematic Review. *Siehe auch: Trivedi et al. 2009: Evidence*	1. Fragestellung: To examine the utility of psychotherapy in managing treatment resistant depression.
	2. Methodik Population: Adult (>18 years) patients with treatment resistant depression. Patients were considered treatment resistant if they reported partial or no remission following treatment with an adequate antidepressant dose for ≥6weeks. Intervention/Komparator: psychotherapy modalities: cognitive therapy, interpersonal therapy, or behavior therapy

Synthesis for Determining the Efficacy of Psychotherapy for Treatment Resistant Depression.	Endpunkt: HAM-D, BDI and QIDS-SR scores Suchzeitraum: Sources were searched from database inception to 07 September 2010 Anzahl eingeschlossene Studien/Patienten (Gesamt): 13 articles evaluating 7 unique treatment comparisons were included. A total of 592 patients were evaluated.
	3. Ergebnisdarstellung *<u>Note</u>: Because of considerable heterogeneity in study designs, a summary estimate of effect was not calculated. Instead, studies were critically analyzed and a qualitative synthesis was conducted.* • Psychotherapy was examined as an augmentation to antidepressants in five studies. Psychotherapy was examined as substitution treatment in two studies. • Compared to active management, two good quality trials showed similar benefit from augmenting antidepressants with psychotherapy • One fair quality and one poor quality trial showed benefit from psychotherapy augmentation • One good and one poor trial found similar benefit from substituting psychotherapy for antidepressants. • One fair quality trial showed lithium augmentation to be more beneficial than psychotherapy.
	4. <u>Fazit der Autoren:</u> *Review demonstrates the utility of psychotherapy in managing treatment resistant depression. However, evidence is sparse and results are mixed. Given that quality trials are lacking, rigorous clinical trials are recommended to guide practice. In the interim, primary care providers should consider psychotherapy when treating patients with treatment resistant depression.*
	5. <u>Hinweise:</u> • Few RCTs exist that adequately address the question of treatment resistant depression. • Most studies appeared to be underpowered to detect moderately large treatment effects. • There was significant heterogeneity in the definition of treatment resistant depression as well as the measures used to determine MDD.
Papakostas et al. 2007 (per Handsuche): Augmentation of Antidepressants with atypical antipsychotic medications for treatmnt-resistant major depressive disorde: a meta-analysis.	1. Fragestellung: To examine the efficacy and overall tolerability of augmenatation of standard antidepressants with atypical antipsychotic agents for treatment-resistant majoe depressive disorder.
	2. Methodik Population: Patients with treatment-resistant major depressive disorder. Intervention: Adjunctive treatment of standard antidepressants with an atypical antipsychotic agent (Risperidon, Olanzapine, Quetiapine, Ziprasidone and Aripiprazole) Komparator: Adjunctive treatment of standard antidepressants with placebo Endpunkt: Remission, response rates Suchzeitraum:Keine Angabe Anzahl eingeschlossene Studien/Patienten (Gesamt): 10 studies with N(total): 1500 outpatients.
	3. Ergebnisdarstellung • Augmentation of standard antidepressants with typical antipsychotic agents resulted in greater remission and response rates than adjunctive placebo treatment in TRD (RR for remission: 1.75; 95%KI: 1.36-2.24; p<0,0001 / RR for response: 1.35; 95%CI: 1.13-1.63; p=0.001). • Pooled remission and response rates for the 2 treamtent groups were 47.4% vs. 22.3% and 57.2% vs. 35.4%, respectively. • No difference in overall discontinuation rate (RR: 1.18; 95%KI: 0.93-

	1.49) or the rate of discontinuation due to inefficacy (RR: 0.66; 95%CI: 0.39-1.13). • Stat. significant difference in favour of placebo between the 2 treatment groups regarding the rate of discontinuation due to adverse events (RR: 3.38; 95%CI: 1.98-5.76; p<0.0001).
	4. Fazit der Autoren: *These results support the utility of augmenting standard antidepressants with atypical antipsychotic agents for treatment-resistant major depressive disorder. An obvious limitation of this work is the absence of data focusing on the use of aripiprazole and ziprasidone. Future shot-as well as ling-term studies comparing the efficacy, safety and tolerability of this versus other adjunctive strategies are warranted.*
	5. Hinweis: • No studies for aripiprazole and ziprasidone (not relevant; no licence in Germany) • Different definitions in studies for remission
Edwars et al. 2013: Lithium or an atypical antipsychotic drug in the management of treatment-resistant depression: a systematic review and economic evaluation	1. Fragestellung: To estimate the clinical effectiveness and cost-effectiveness of augmentation of selective serotonin reuptake inhibitor (SSRI) antidepressant therapy with either lithium or an AAP drug in the management of people with treatment-resistant unipolar depression, defined as failure to respond to two or more antidepressant drugs in their current episode of depression.
	2. Methodik Population: Patients with treatment-resistant depression (TRD) are those with major depressive disorder that has not responded adequately to treatment. Intervention: SRI (defined as citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine or sertraline), *plus* an AAP drug (also known as second-generation antipsychotic, and defined as amisulpride, aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone or ziprasidone). Komparator: SRI (defined as citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine or sertraline), *plus* lithium (lithium carbonate or lithium citrate or lithium). **Subgroup analyses** The a priori subgroup analyses deemed to be most important were as follows: - different durations of depression (i.e. time since first onset of current episode of depression) - class of previous antidepressants (e.g. SSRI or tricyclic antidepressant) - sex (i.e. male and female) - age (i.e. those < 75 years and those ≥ 75 years) - people with different severities of depression (i.e. based on trial entry HAMD score13). Endpunkte: response (measured by a reduction of at least 50% in HAMD13 or MADRS14 score); remission (using individual trial definitions); mean change from baseline MADRS14 score; quality of life (QoL) as reported using a validated QoL rating scale25 [e.g. Short Form questionnaire-36 items (SF-36)]; adverse events (total number of events, and the individual adverse events deemed most burdensome to patients); withdrawals (all cause) as a surrogate outcome for adherence to medication; relapse rate; mortality; cost-effectiveness. Suchzeitraum (Aktualität der Recherche): Databases searched were Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, MEDLINE, PsycINFO and NHS Economic Evaluation Database (NHS

	EED). All databases were searched from inception to August 2011. Additional data were obtained from manufacturers. Anzahl eingeschlossene Studien/Patienten (Gesamt): 12 RCTs were identified in the review of clinical effectiveness literature; 10 considered SSRI + AAP compared with SSRI + placebo/no treatment, one considered SSRI + AAP compared with SSRI + lithium and one considered SSRI + lithium compared with SSRI + placebo. Six of the 10 SSRI + AAP trials were included in the primary analysis; the remaining four RCTs were included in a class-based sensitivity analysis. Of the trials considering lithium augmentation as a comparator, only one was included in the primary analysis. All six trials considering augmentation with an AAP included in the primary analysis evaluated fluoxetine (SSRI) + olanzapine (AAP). Furthermore, the lithium trial included in the primary analysis used fluoxetine as the background SSRI in both the comparator group and lithium augmentation group.
	3. Ergebnisdarstellung: **Results for SSRI plus atypical antipsychotic vs. SSRI alone (pairwise comparison)** • Five RCTs reported response based on the MADRS and the remaining RCT used the HAMD Scale. The results of the meta-analysis demonstrated a statistically significant benefit for fluoxetine + olanzapine over fluoxetine alone (OR: 1.48; 95% CI 1.13 to 1.94) with a moderate level of statistical heterogeneity (I^2 = 53%; p = 0.07). • Five RCTs reported the outcome of remission. Meta-analysis demonstrated a statistically significant increase in remissions in patients treated with olanzapine + fluoxetine compared with fluoxetine alone (OR: 1.77; 95% CI 1.27 to 2.47) with no statistical heterogeneity (I^2=0%; p = 0.75). • Data on relapse rates were not available for analysis. • Four RCTs reported least square mean difference (MD) from baseline in MADRS score at study end point. Meta-analysis resulted in a statistically significant MD of − 2.04 (95% CI: − 3.25 to − 0.82) in favour of fluoxetine + olanzapine. However, there was a high level of heterogeneity that was statistically significant (I^2 = 73%; p = 0.01). • Meta-analysis of five trials found that olanzapine augmentation therapy was associated with a non-statistically significant increase in discontinuations (OR: 1.25; 95% CI: 0.91 to 1.71) with no statistical heterogeneity (I^2=0%; p = 0.51). **SSRI plus lithium vs. SSRI plus placebo response (pairwise comparison)** • The single trial comparing fluoxetine + lithium with fluoxetine alone used two definitions of response, one prespecified primary analysis and one post hoc analysis. Results of the primary and post hoc analyses for response data indicated a non-significant trend in favour of lithium augmentation compared with SSRI alone (OR: 1.48; 95% CI 0.37 to 5.95 and OR: 3.85; 95% CI 0.80 to 18.62, respectively). • Data on remission or relapse rates were not available. **Mixed-treatment comparison: SSRI plus atypical antipsychotic vs. SSRI plus lithium** • Seven RCTs were included in the MTC: six for SSRI + AAP compared with SSRI alone and one RCT for SSRI + lithium compared with SSRI alone. Two separate analyses for the outcome of response were conducted because the trial informing the comparison with lithium reported response using two criteria. Analyses of response using the lithium primary analysis and the lithium post hoc analysis data showed a non-significant trend in favour of treatment with lithium (OR 1.29; 95% credible interval (CrI) 0.11 to 5.32 and OR 4.15; 95% CrI 0.25 to 20.34,

	respectively). • Five trials were included in the analysis for mean change in MADRS (four RCTs were AAPs and one was a lithium RCT). The random-effects model resulted in a weighted MD of − 1.47 (95% CrI − 9.10 to 6.41) for the mean change in MADRS score from baseline for fluoxetine + lithium compared with fluoxetine + olanzapine, which suggests a statistically non-significant trend in favour of lithium augmentation. However, the wide 95% CrI indicates a high level of uncertainty in this estimate of treatment effect and so the results should be interpreted with caution. • Six trials reported data on all-cause withdrawals. The fixed-effects model results suggested a statistically non-significant trend in favour of augmentation with lithium (OR 0.74; 95% CrI 0.10 to 2.66) compared with augmenting with AAP. • Various sensitivity analyses were carried out, including analyses assuming class effects of SSRIs and AAPs, analysis of RCTs in which patients had experienced two or more failures to antidepressants in their current episode, and analysis of RCTs reporting response based on MADRS score. Results of most sensitivity analysis were consistent with the results of the primary analysis. However, the result of the sensitivity analysis assuming a class effect for SSRIs and AAPs for the outcome of mean change in MADRS differed from the primary analysis, identifying a statistically non-significant trend in favour of treatment with SSRI + AAP (MD: 1.27; 95% CrI − 1.88 to 4.68). <u>Qualität der zugrundeliegenden Studien:</u> • All 12 of the included RCTs were assessed for quality using the Cochrane risk-of-bias tool. • In the overall assessments for each study, as well as the majority of the assessments for the individual outcomes of interest,all of the trials were rated as unclear risk of bias..
	4. Anmerkungen/Fazit der Autoren: *The results of this review support the conclusion that augmentation of SSRIs with lithium or AAP is likely to be beneficial in people with TRD, defined as a failure to respond to two or more antidepressants in the current episode of depression. However, based on the limited number of RCTs identified, the clinical evaluation suggests there is no statistically significant difference between the two augmentation strategies. There is a general paucity of trial data available in patients with TRD for SSRI + lithium and SSRI + AAP.* 5. Hinweise durch FB Med: • The major weakness of this analysis is the lack of head-to-head data on the effectiveness of the comparison of SSRI + AAP with SSRI + lithium in patients with TRD.
Carvalho, 2014: The Integrative Management of Treatment-Resistant Depression: A comprehensive Review and Perspectives. *Siehe auch*: **Wright et al. 2013:** Augmentation with Atypical Antipsychotics for Depression: A Review of Evidence-Based Support from the	1. Fragestellung: The review summarizes the available evidence for various pharmacological approaches to TRD.
	2. Methodik Population: Patientes with treatment-resistant depression (TRD) Intervention/Komparator: Different switching therapies (Changing to an SNRI versus Another SSRI; Switching to Bupropion; Switching to MirtazapineI; Combination strategies such as Mirtazapine and/or Mianserin plus Newer-Generation Antidepressants; SSRI plus Bupropion; Augmentation Strategies such as Lithium) Endpunkt: Siehe Ergebnisteil Suchzeitraum (Aktualität der Recherche): The MEDLINE/PubMed, EMBASE and ClinicalTrials.gov electronic databases were searched from inception to October 1, 2013, for randomized controlled trials (RCT), relevant open-label trials, meta-analyses and ongoing trials of

Medical Literature.	pharmacological and psychotherapeutic approaches to TRD. Anzahl eingeschlossene Studien/Patienten (Gesamt): Siehe Ergebnisteil
	3. Ergebnisdarstellung **Changing to an SNRI vs. another SSRI:** • Previous meta-analyses have consistently reported that venlafaxine is a somewhat more effective antidepressant than the SSRIs as a class. • More recently, 3 other SNRIs – milnacipran, duloxetine and desvenlafaxine – have also been made available. Some trials have compared switching to an SNRI with intraclass switches. • The first study was an RCT of 122 inpatients or day hospital patients who had 2 unsuccessful antidepressant trials in their current affective episode. After 4 weeks of either paroxetine or venlafaxine, the venlafaxine group demonstrated a remission rate of 37% compared with the remission rate of 18% in the paroxetine group ($p = 0.01$). • The second double-blind study followed 406 patients who failed to respond to ongoing SSRI treatment. Unlike the prior trial, this study demonstrated no advantage of venlafaxine XR with regard to the primary outcome measure, in this case the HDRS-21. • In the large-scale ARGOS trial, 3,097 people who were unsuccessfully treated with an SSRI were randomized to venlafaxine XR or another newer-generation antidepressant (most commonly an SSRI or mirtazapine). After 24 weeks, HDRS-17 remission rates were higher in the venlafaxine XR group (59.3%) than in the other group (51.5%). This relatively small clinical effect was nonetheless statistically significant. • In the STAR * D level 2 trial, sertraline, venlafaxine XR and bupropion sustained release were compared as second-step switching therapies among 727 participants who had unsatisfactory clinical results or intolerance to a citalopram trial. The results for the 3 groups did not significantly differ at the study endpoint. • Romera et al.studied a sample of 281 MDD patients who failed to achieve a reduction of at least 30% in depressive symptoms following a 4-week escitalopram (10 mg/day) trial. This sample had significant pain symptoms at baseline (>30 mm overall pain score on the visual analog scale). These participants were randomized to duloxetine 60–120 mg/day (early switch) or continued on escitalopram 10 mg/day (conventional switch) with nonresponders at week 8 switched to duloxetine. These two switching protocols did not differ regarding remission rates or time to achieve either response or remission after 16 weeks. However, an early switch to duloxetine resulted in lower pain scores and higher functional improvement by the study endpoint. **Switching to Bupropion:** • There are no methodologically sound studies to support this strategy. • The use of bupropion, a dopamine and norepinephrine reuptake inhibitor, as a switching strategy for SSRI-resistant depression was investigated in the STAR * D trial discussed previously, which does not favor this agent over another SSRI or venlafaxine. **Switching to Mirtazapine:** • One large RCT compared the efficacy of switching to mirtazapine with switching to a second SSRI in SSRI nonresponders. In this trial, 250 patients who had not responded to an SSRI other than sertraline were randomized to receive either sertraline or mirtazapine and followed up for 8 weeks. At the endpoint, the remission rates were 38% for mirtazapine and 28% for sertraline. Even if this difference did not reach statistical significance, the mirtazapine group experienced a significantly faster response and remission. • As one of the comparators of the ARGOS trial, mirtazapine was compared with a second SSRI as well as with venlafaxine XR as a second agent following SSRI failure. In this trial, the venlafaxine group had higher response and remission rates at the study endpoint. The

response and remission rates for the SSRI and mirtazapine groups appeared similar.

- The use of mirtazapine was compared with the use of nortriptyline following antidepressant failure in the STAR * D trial, although for participants with more significant TRD. Of the 235 participants entering this step of the trial, 12.3% of the mirtazapine group reached
- remission, compared with 19.8% of the nortriptyline group; this difference again did not reach statistical significance. While the use of mirtazapine as a second-step agent for TRD is therefore understudied, the available evidence indicates that this agent may hold promise for effective remission after SSRI failure.

Combination Strategies

Mirtazapine and/or Mianserin plus Newer-Generation Antidepressants:

- The efficacy of the mianserin combination for TRD has been investigated in at least 2 RCTs. Ferreri et al. randomized a sample of 104 patients who had not responded to a 6-week fluoxetine (20 mg/day) trial to one of the following arms: fluoxetine 20 mg plus mianserin 60 mg; fluoxetine 20 mg plus placebo; or mianserin 60 mg plus placebo. The remission rates were: 44% for the combination, 36% for the mianserin-plus-placebo group and 18% for the fluoxetine-plus-placebo group. The number needed to treat (NNT) for the combination was 4 patients for 1 remission beyond what would be expected for fluoxetine alone.
- A more recent RCT has shown that adding mianserin to sertraline nonresponders offered no advantage over adding placebo. However, the initial trial of sertraline monotherapy was brief and a dose increment of sertraline was carried out 2 weeks prior to randomization, thereby confounding the interpretation of the results.
- Carpenter et al. randomized 26 subjects who had got an SSRI to receive either mirtazapine augmentation (30 mg/day) or placebo. After 4 weeks, subjects who received adjunctive mirtazapine showed significantly higher HDRS remission rates (45.5 vs. 13.3%); these data translate to an NNT of 3 for remission, but the small sample size limits the generalizability of the findings.
- A total of 109 patients who had not responded to 3 sequential treatment trials in the STAR * D trial were randomly assigned to treatment with either a mirtazapineplus- venlafaxine combination or the MAOI tranylcypromine, as mentioned previously. Neither treatment was particularly efficacious, with final remission rates of 7 and 14% for the tranylcypromine and antidepressant combination groups, respectively. Nevertheless, the combination strategy was associated with significantly lower attrition secondary to side effects.

SSRI plus Bupropion:

- When compared with TCA, important advantages include: (1) bupropion has a more favorable side effect and tolerability profile than TCA, and (2) bupropion may help counteract the adverse effects of SSRI on sexual function. Two open-label active-comparator trials have been published, and when considered together, these studies provide only limited support for the strong clinical enthusiasm for this combination.

Augmentation Strategies

Lithium:

- The first reported trial of lithium augmentation by de Montigny et al. described its efficacy in combination with TCA.
- Metaanalysis by Crossley and Bauer: The efficacy of lithium as an augmenting agent was confirmed, with an overall odds ratio for response of 3.1 (1.8–5.4) favoring lithium; pooling the results, the NNT to achieve a response was 4.

	• More recently, Nierenberg et al. performed an RCT of lithium augmentation of nortriptyline in a sample of TRD participants who had failed to respond to several previous antidepressant trials. There were no significant differences between lithium and placebo augmentation by the end of the trial. No RCT has been published since the completion of this meta-analysis. • In the STAR * D trial, 142 patients who had failed to respond to 2 sequential antidepressant trials were randomized to either lithium or T 3 augmentation. In that trial, only 15.9% of the lithium-treated patients remitted, compared with 24.7% of the patients treated with T 3 augmentation.
	4. Fazit der Autoren: *The success of switching to a different antidepressant following a first-line agent is supported by evidence, but there is limited evidence for effective combination strategies. Lithium and T 3 augmentation of TCA have the strongest evidence base for successful treatment of TRD. The use of augmentation of newer-generation antidepressants with atypical antipsychotics is supported by a growing evidence base. Current evidence supports CT as an effective strategy for TRD. There is a need for additional large-scale RCT of TRD. The development of new antidepressants targeting novel pathways opens a promising perspective for the management of TRD.*
Maneeton et al. 2013: 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.
	2. Methodik Population: Adults with major depressive disorder (MDD) Intervention/Komparator: Bupropion and Venlafaxin Endpunkt: (1) severity of depression; (2) response rate; (3) remission rate; (4) overall discontinuation rate; or (5) discontinuation rate due to adverse events. Suchzeitraum (Aktualität der Recherche): The 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
	3. Ergebnisdarstellung • The pooled mean changed scores of the bupropion-treated group were comparable to those of the venlafaxine-treated group with standardized mean differences of 0.05 (−0.16 to 0.26). • The overall response and remission rates were similar with the RRs of 0.92 (0.79–1.08) and 0.97 (0.75–1.24), respectively. • The pooled overall discontinuation rate and discontinuation rate due to adverse events were not different between groups with the RRs of 1.00 (0.80–1.26) and 0.69 (0.44–1.10), respectively. <u>Qualität der zugrundeliegenden Studien:</u> • Based on the Cochrane's bias assessment, risks of bias were assessed. Any study with two risks or more was excluded. → Since all trials had the low-risk of biases, all their data were analyzed.
	4. Fazit der Autoren: *According to the findings provided from these three RCTs, bupropion XL was as effective as venlafaxine XR for adult MDD patients. The equivalent dropout rate due to adverse events indicates the comparable tolerability of both active agents. Based on the overall discontinuation rates, which took into account both the efficacious benefit and risk from adverse events, these agents appeared to have comparable acceptability. Based on the CSFQ scores, a trend indicated*

	that bupropion is less likely to cause treatment-emergent sexual dysfunction. However, these outcomes should be considered as initial findings. Further well-defined clinical trials in this field should be conducted to confirm these findings. Additionally, further systemic reviews of bupropion in the treatment of MDD compared with other antidepressants, including SSRIs, may be useful. 5. Anmerkungen durch FB Med: • Small number of RCTs included in the meta-analysis
Badley und Lenox-Smith, 2013: Does adding noradrenaline reuptake inhibition to selective serotonin reuptake inhibition improve efficacy in patients with depression? A systematic review of metaanalyses and large randomised pragmatic trials.	1. Fragestellung: This review aims to examine the evidence of including noradrenaline reuptake inhibition with serotonin reuptake inhibition with respect to increasing efficacy in the treatment of depression
	2. Methodik Population: Adults with depression Intervention: Second-generation SNRI antidepressants (duloxetine, desvenlafaxine, milnacipran and venlafaxine) Komparator: SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) Endpunkt: Remission rates, response rates and mean differences in rating scale score, since remission is the primary goal of antidepressant treatment (National Institute for Health and Clinical Excellence, 2010), the review states to focus on the remission outcomes. Suchzeitraum (Aktualität der Recherche): Ovid, Medline, Embase and PsychInfo were searched for meta-analyses comparing second-generation SNRI antidepressants (duloxetine, desvenlafaxine, milnacipran and venlafaxine) to SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) in the treatment of depression. Kein Suchzeitraum angegeben. Anzahl eingeschlossene Studien/Patienten (Gesamt): Fifteen meta-analyses of RCT summary data were included and seven meta-analyses of individual patient data.
	3. Ergebnisdarstellung *Venlafaxine compared to pooled SSRIs:* • Venlafaxine was consistently found to be superior in remission rates compared to pooled SSRIs with OR for remission ranging from 1.12–1.43. • Venlafaxine was found to be statistically significantly superior in remission rates to pooled SSRIs across all depression levels examined with the greatest OR of 1.55 (95% CI 1.10–2.18) being in those with the highest severity of baseline symptoms (HDRS17≥30). *Venlafaxine compared to individual SSRIs:* • Allgemein: Fluoxetine was the most common comparator SSRI • The patient-level meta-analysis found a 6.6% remission advantage for venlafaxine resulting in a NNT of 16 and ORs for remission ranged from 1.16–1.42. Only the effect found in the analysis of published trials (14 RCTs) was not statistically significant but that was borderline (OR 1.16; 95% CI 0.99–1.34). • Paroxetine was the next most studied comparator SSRI. The patient-level analysis found a 4.6% remission advantage for venlafaxine that bordered on statistical significance (95% CI –0.04–0.097) and ORs for remission ranged from 1.23–1.49 but not all were statistically significant. • Remission rates compared to sertraline were generally in favour of venlafaxine but not statistically significantly so. • No significant difference was found in remission rates between

	venlafaxine and fluvoxamine from the meta-analysis of two RCTs. • ORs for remission favoured escitalopram over venlafaxine (two RCTs or 483 patients) and venlafaxine over citalopram (two RCTs or 539 patients), but neither difference was statistically significant. *Duloxetine compared to pooled SSRIs:* • A remission rate in favour of duloxetine was found OR 1.1≥1 (95% CI 0.91–1.34) from the analysis of summary data from nine RCTs but this was not statistically significant. The two patient-level meta-analyses found significantly greater remission rates with duloxetine compared to pooled SSRIs only in patients with moderate to severe depression. *Duloxetine compared to individual SSRIs:* • Paroxetine was the most studied comparator SSRI. An OR for failure to remit of 1.02 was found which was not statistically significantly different between treatments. • Compared to fluoxetine, the OR for failure to remission from two RCTs was in favour of duloxetine (OR 0.64; 95% CI 0.35–1.17) but was not statistically significantly different. • ORs for remission favoured escitalopram over duloxetine in data from three RCTs but were not statistically significantly different. *Pooled SNRIs versus pooled SSRIs:* • One meta-analysis of RCT summary data compared pooled SNRIs with pooled SSRIs using data from 15 fully published RCTs. Five RCTs compared duloxetine to SSRIs and 10 compared venlafaxine to SSRIs. Fluoxetine was the comparator SSRI in five RCTs, paroxetine in four, escitalopram in three and sertraline in three. ORs for remission and remission rates were significantly greater with the SNRIs than SSRIs *Escitalopram vs pooled SNRIs:* • One meta-analysis of individual patient data (N=132) compared pooled SNRIs (duloxetine and venlafaxine) to escitalopram in patients who had failed to respond to a previous antidepressant. Escitalopram was associated with greater remission rates than SNRIs. • One meta-analysis of individual patient data compared SMD in HDRS17 change using data from five RCTs including 1598 patients comparing escitalopram to pooled SNRIs (duloxetine and venlafaxine). A small advantage for escitalopram was found that was not statistically significantly different.
	4. Fazit der Autoren: *There is sufficient current evidence that demonstrates an increase in efficacy, when noradrenaline reuptake is added to serotonin (5-HT) reuptake, to suggest that patients with severe depression or those who have failed to reach remission with a SSRI may benefit from treatment with a SNRI.*
Lopes et al. 2013: Antidepressant combination for major depression in incomplete responders—a systematic review.	1. Fragestellung: The objective of this study was to perform a systematic review and meta-analysis of studies that assessed the effect of antidepressant combination for major depression inpatients with incomplete response to an initial antidepressant
	2. Methodik Population: Participants were adult out- or inpatients (aged 18–65 years) with major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) criteria. Intervention:Combina tion of antidepressants Komparator: Single antidepressant Endpunkt: Remission, response, safety

	Suchzeitraum (Aktualität der Recherche): Studies were retrieved from PubMed (1966–February, 2012), Cochrane Library (–February, 2012), Embase (1980–February, 2012), PsycINFO (1980–February, 2012), Lilacs (1982–February, 2012), clinical trials registry, thesis database (www.capes.gov.br), and secondary references. Anzahl eingeschlossene Studien/Patienten (Gesamt): Fünf Studien mit N=483 Patienten
	3. Ergebnisdarstellung • Meta-analysis was not performed due to the small number of studies, the inconsistency in the direction of effect and the possible instability of effect size. • Only two small trials reported benefits of adding a second antidepressant to the initial antidepressant. • Dropouts due to side effects were not reported in three studies. • Only limited kinds of combination, involving mianserin, mirtazapine and desipramine were studied. Some properties of the first two drugs such as the anxiolytic, sedative, and orexigenic effects can mimic depression improvement. *Qualität der Studien:* One study was considered to have a low risk of bias and the other four an unknown risk. The risk was considered unknown because of the absence of an adequate description of sequence generation and/orallocation concealment. All studies had low risk of performance, attrition, and detection bias. Three studies evaluated antidepressants (mirtazapine and mianserin) developed by the same pharmaceutical industry.The side effects of these agents, e.g. sedation could interfere with blinding in aplacebo-controlled study. In addition, the 5HT2 and 5HT3 antagonism of mianserin and mirtazapine could neutralize the adverse events related to fluoxetine or other SSRIs such as nausea, loss of appetite, insomnia and sexual dysfunction. In the Fava trials, the anticholinergic effect of desipramine could also interfere with blinding.
	4. Fazit der Autoren: *The practice of using a combination of antidepressants for major depression in incomplete responders is not warranted by the literature*
Tuner et al. 2014: A systematic review and meta-analysis of the evidence base for add-on treatment for patients with major depressive disorder who have not responded to antidepressant treatment: A European perspective.	1. Fragestellung: This meta-analysis reviewedall published peer-reviewed evidence for the efficacy of EU-licensed therapies in patients with MDD and an inadequate response to antidepressant monotherapy.
	2. Methodik Population: Patients with major depressive disorder (MDD) with an inadequate response to antidepressants Intervention: Antidepressant Komparator: Placebo, other antidepressant Endpunkt: Response, remission Suchzeitraum (Aktualität der Recherche): A protocol was written for this meta-analysis prior to the initiation of the literature search which was conducted in the Cochrane Central Register of Controlled Trials (CENTRAL), the Excerpt a Medica Database (EMBASE), and the Index Medicus database (MEDLINE). The search was restricted to English-language papers and abstracts, and all searching was completed in November 2011 with no restriction on date of publication. Anzahl eingeschlossene Studien/Patienten (Gesamt): 12 papers were found to report RCTs of EU-licensed add-on treatments for patients with MDD with an inadequate response to their indexantidepressant

	treatment; seven of these trials reported response and remission in such a way that allowed quantitative analysis.
	3. Ergebnisdarstellung Allgemein: • Two trials compared add-on lithium with placebo, one trial comparedadd-on mianserin with placebo, one trial compared add-on mirtazapine with placebo, two trials compared add-on extended release (XR) quetiapine fumarate with placebo, and one trial compared add-on SAMe with placebo • None of the types of add-on treatment (lithium, atypical antipsychotic, antidepressant, or SAMe) were assessed in more than three trials in this systematic review. *Adjusted indirect comparison results* • The results of the adjusted indirect comparisons between classes of add-on intervention (i.e. antidepressant, lithium, atypical antipsychotic, and SAMe) indicated that there was an equal likelihood of achieving response or remission with add-on quetiapine XR (150 mg or 300 mg) versus an antidepressant, lithium, or SAMe, or with an add-on antidepressant versus lithium or SAMe. However, when compared with add-on lithium, patients treated with add-on SAMe were significantly more likely to achieve response.
	4. Fazit der Autoren: *There is clearly a requirement for further high-quality research regarding the use of add-on treatment in patients with MDD and an inadequate response to antidepressant therapy.* 5. Anmerkungen: • low overall number of selected studies, and those trials that were included had small patient populations (n values ranged from 26–73) (apart from the two quetiapine XR studies and the mianserin study). • high degree of heterogeneity in the studies of antidepressant combinations, which led to uncertainty concerning the robustness of the pooled results • studies included in this meta-analysis also varied widely in terms of their duration, had differing response and remission criteria, and also had different levels of MDD severity at baseline.
Kriston et al. 2014: Efficacy and acceptability of acute treatments for persistent depressive disorder: a network metaanalysis.	1. Fragestellung: To synthesize the available evidence on the relative efficacy and acceptability of specific treatments for persistent depressive disorder.
	2. Methodik Population: Patients with persistent depressive disorder Intervention/Komparator: Acute pharmacological, psychotherapeutic, and combined interventions with each other or placebo Endpunkt: Proportion of patients who responded to (efficacy) or dropped out from (acceptability) the allocated treatment. *Hinweis*: Data synthesis was performed with network meta-analysis Suchzeitraum (Aktualität der Recherche): Databases were searched up to January 2013 for RCTs. A primary search was performed in 2010 and an update in 2013. Anzahl eingeschlossene Studien/Patienten (Gesamt): A network of 45 trials that tested 28 drugs included data from 5,806 and 5,348 patients concerning efficacy and acceptability, respectively. A second network of 15 trials that tested five psychotherapeutic and five combined interventions included data from 2,657 and 2,719 patients concerning efficacy and acceptability, respectively.
	3. Ergebnisdarstellung • Among sufficiently tested treatments, fluoxetine (OR: 2.94), paroxetine

	(3.79), sertraline (4.47), moclobemide (6.98), imipramine (4.53), ritanserin (2.35), amisulpride (5.63), and acetyl-l-carnitine (5.67) were significantly more effective than placebo. • Pairwise comparisons showed advantages of moclobemide (2.38) and amisulpride (1.92) over fluoxetine. • Sertraline (0.57) and amisulpride (0.53) showed a lower dropout rate than imipramine. • Interpersonal psychotherapy with medication outperformed medication alone in chronic major depression but not in dysthymia. • Evidence on cognitive behavioral analysis system of psychotherapy plus medication was partly inconclusive. • Interpersonal psychotherapy was less effective than medication (0.48) and cognitive behavioral analysis system of psychotherapy (0.45). Several other treatments were tested in single studies. <u>Qualität der Studien:</u> Overall risk of bias was rated as low for 12 studies, as unclear for 31 studies, and 13 studies were judged to be prone to a high risk of bias. Most studies used an adequate blinding (42 of 56), addressed incomplete data adequately (38 of 56), and were free of selective outcome reporting (43 of 56) and other risk of bias (41 of 56); yet only 10 studies reported an adequate concealment of allocation and only 19 studies reported an adequate generation of the allocation sequence.
	4. Fazit der Autoren: *Several evidence-based acute pharmacological, psychotherapeutic, and combined treatments for persistent depressive disorder are available with significant differences between them.* 5. Anmerkungen: • Limited number of studies
Wang et al. 2013: Comparative efficacies of fluoxetine and paroxetine in major depression across varying acute-phase treatment periods: A meta-analysis.	1. Fragestellung: A meta-analysis to ascertain the efficacy of fluoxetine versus paroxetine for depression by varying acutephase treatment periods.
	2. Methodik Population: Patients with depression Intervention/Komparator: fluoxetine vs. paroxetine Endpunkt: response rate, dropout rate Suchzeitraum (Aktualität der Recherche): PubMed, CCTR, Web of Science, Embase, CBM-disc, and CNKI were searched up to March 2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 17 studies were included with N= 3,110 patients. Three treatment period subgroups were created: 6, 8/10, and 12 weeks.
	3. Ergebnisdarstellung • In the 6-week subgroup, paroxetine was more efficacious than fluoxetine (OR: 0.74; P < 0.05). In the 8/10-week subgroup, two drugs displayed comparative efficacy (OR, 0.85; P > 0.05). • In the 12-week subgroup, fluoxetine was more efficacious than paroxetine (OR: 1.25; P < 0.05). • There were no significant differences in acceptability. • Significant heterogeneity and potential publication bias did not exist.
	4. Fazit der Autoren: *Patients' economic conditions, individual preference, and side effects of fluoxetine and paroxetine can be obstacles of successful treatment. Inappropriate acute-phase treatment, such as inadequate treatment periods, may result in pseudoresistance. Clinicians should take these information into consideration when prescribe fluoxetine or paroxetine for patients. Our results can aid*

	clinicians in making an optimal treatment plan to increase odds of response. 5. Anmerkungen: • Most of the selected RCTs in this meta-analysis did not report adequate information about blinded outcome assessment.

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library (Cochrane Database of Systematic Reviews) am 04.03.2014

Suchschritt	Suchfrage	Treffer
#1	MeSH descriptor: [Depressive Disorder] explode all trees	7070
#2	MeSH descriptor: [Depression] explode all trees	4922
#3	MeSH descriptor: [Mood Disorders] explode all trees	8629
#4	depressive or depressed or depression or dysthymi*:ti (Word variations have been searched)	15815
#5	unipolar and disorder*:ti (Word variations have been searched)	24
#6	affective and disorder*:ti (Word variations have been searched)	410
#7	mood and disorder*:ti (Word variations have been searched)	245
#8	#1 or #2 or #3 or #4 or #5 or #6 or #7 from 2009 to 2014	5806

Cochrane Library (Database of Abstracts of Reviews of Effect und Health Technology Assessment Database) am 04.03.2014

Suchschritt	Suchfrage	Treffer
#1	MeSH descriptor: [Depression] explode all trees and with qualifier(s): [Drug therapy - DT]	1626
#2	MeSH descriptor: [Depressive Disorder] explode all trees and with qualifier(s): [Drug therapy - DT]	3735
#3	depressive or depressed or depression or dysthymi*:ti (Word variations have been searched)	15815
#4	affective disorder*:ti	958
#5	mood disorder*:ti	1098
#6	unipolar disorder*:ti	120
#7	MeSH descriptor: [Antidepressive Agents] explode all trees	4744
#8	serotonin and inhibitor*:ti (Word variations have been searched)	506
#9	#1 or #2	5283
#10	#3 or #4 or #5 or #6	17287
#11	(antidepressive* or antidepressant* or monotherap* or polytherap* or pharmacotherap*):ti	6010
#12	#7 or #8 or #11	9975
#13	#10 and #12	3497
#14	#9 or #13 from 2009 to 2014	1446
#15	bipolar:ti	2102
#16	(children or adolescen* or pediatric* or teen* or juvenile*):ti	39595
#17	#14 not #15	1372
#18	#17 not #16	1320

MEDLINE (PubMed) am 04.03.2014

Suchschritt	Suchfrage	Treffer
#1	Search "depressive disorder/drug therapy"[MeSH Major Topic]	13329
#2	Search "depression/drug therapy"[MeSH Major Topic]	6208
#3	Search (((depression[Title]) OR depressive[Title]) OR depressed[Title]) OR dysthymi*[Title]	94530
#4	Search affective disorder*[Title]	4290

#5	Search mood disorder*[Title]	2267
#6	Search unipolar disorder*[Title]	26
#7	Search ((((((((((((treatment*[Title]) OR therapy[Title]) OR therapies[Title]) OR therapeutic[Title]) OR antidepressive*[Title]) OR antidepressant*[Title]) OR monotherap*[Title]) OR polytherap*[Title]) OR pharmacotherap*[Title]) OR effect*[Title]) OR efficacy[Title]) OR treating[Title]) OR treated[Title]) OR treat*[Title]	3034716
#8	Search (serotonin[Title]) AND inhibitor*[Title]	2826
#9	Search (#3 OR #4 OR #5 OR #6)	100752
#10	Search (#7 OR #8)	3036285
#11	Search (#9 AND #10)	24322
#12	Search medline[sb]	21002350
#13	Search (#11 NOT #12)	2522
#14	Search (#1 OR #2)	19319
#15	Search (#13 OR #14)	21841
#16	Search ((((children[Title]) OR adolescen*[Title]) OR pediatric*[Title]) OR teen*[Title]) OR juvenile*[Title]	579349
#17	Search (#15 NOT #16)	21137
#18	Search ((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract])))	167678
#19	Search (#17 AND #18)	934
#20	Search (#15 NOT #16) Filters: Meta-Analysis	429
#21	Search (#19 OR #20)	1047
#22	Search (comment[Publication Type]) OR letter[Publication Type]	1062277
#23	Search (#21 NOT #22)	1027
#24	Search "Cochrane Database Syst Rev"[Journal]	9816
#25	Search (#23 NOT #24)	979
#26	Search (#23 NOT #24) Filters: published in the last 5 years	453

MEDLINE (PubMed) nach Leitlinien am 04.03.2014

Suchschritt	Suchfrage	Treffer
#23	Search "depressive disorder"[MeSH Terms]	78078
#24	Search "depression"[MeSH Terms]	72608
#27	Search "Mood Disorders"[Mesh:NoExp]	10404
#28	Search (((depressive[Title]) OR depressed[Title]) OR depression[Title]) OR dysthymi*[Title]	94530
#29	Search (unipolar[Title]) AND disorder*[Title]	378

#30	Search (affective[Title]) AND disorder*[Title]	4786
#31	Search (mood[Title]) AND disorder*[Title]	3213
#32	Search ((((((#23) OR #24) OR #27) OR #28) OR #29) OR #30) OR #31	180973
#33	Search guideline*[Title]	48594
#34	Search (#32) AND #33	516
#35	Search ((((((#23) OR #24) OR #27) OR #28) OR #29) OR #30) OR #31 Filters: Practice Guideline	152
#36	Search ((((((#23) OR #24) OR #27) OR #28) OR #29) OR #30) OR #31 Filters: Practice Guideline; Guideline	164
#37	Search (#34) OR #36	600
#38	Search (#34) OR #36 Filters: published in the last 5 years	187

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Anlage 1: Zusammenfassende Ergebnisse der LL-Recherche zur Therapie der Depression

Kernaussage ⇩	EVK ⇩	EMK ⇩	Leitlinie ACP	AKDÄ	CPA	CTF	ICSI	NICE	NZGG
Pharmakotherapie – Antidepressiva allgemein (KE sieheTabelle 12)									
Jede Behandlungsentscheidung sollte die Symptomatik, psychosoziale Einfluss-faktoren, Komorbiditäten, Vorgeschichte und Patientenpräferenzen einbeziehen.	⇧ -	- ⇔	☑	- -	- -	- -	✓ -	- -	- ✓
Leichte Depression Zur Primärbehandlung einer leichten Depression werden Antidepressiva nicht empfohlen.	-	⇔	-	-	-	-	-	✓	-
Zur Primärbehandlung einer leichten Depression kann eine alleinige Psychotherapie bzw. die Durchführung psychosozialer Maßnahmen versucht werden.	-	⇔	-	☑	-	-	☑	-	✓
Mittelschwere Depression Bei mittelschwerer Depression werden Antidepressiva oder Psychotherapie empfohlen (abhängig von Vorgeschichte, Kontraindikationen, Präferenzen, u. a.).	⇔-⇧⇧ -	- ⇧	- -	☑	- -	- -	✓ -	- -	- ✓
Bei mittelschwerer Depression sollte routinemäßig vor einer psychologischen Intervention eine Therapie mit Antidepressiva angeboten werden.	-	⇧	-	-	-	-	-	✓	-
Schwere / mittelschwere Depression mit unzureichendem Behandlungserfolg Bei schwerer bzw. mittelschwerer Depression sollte ein kombinierter Einsatz von Antidepressiva und Psychotherapie erwogen werden.	⇔-⇧⇧ -	- ⇧	- -	- -	- -	- -	✓ -	- ✓	- ✓
Immer zu beachten sind Kontraindikationen, potenzielle Interaktionen und Nebenwirkungen der Medikamente sowie Begleiterkrankungen. Ein regelhaftes aktives Monitoring und Case-Management sind wichtig.	- ⇔-⇧	⇔ ⇔-⇧	☑	☑	- ✓	- -	☑	✓ -	- ✓
Der Patient muss über die Bedeutung einer regelmäßigen Einnahme und mögliche Auswirkungen eines Therapieabbruchs informiert werden. Bei Therapiewechsel muss eine langsame Ausschleichung des alten und Aufdosierung des neuen Medikamentes erfolgen (Gefahr von Wechselwirkungen, Serotoninsyndrom).	-	⇔	☑	-	-	-	-	✓	-

EVK: Evidenzkategorie; EMK: Empfehlungskategorie; KE: Kernempfehlung

✓ Die Leitlinie unterstützt die Kernaussage im Rahmen einer konkreten Kernempfehlung.

☑ Die Leitlinie unterstützt die Kernaussage im Hintergrundtext, jedoch nicht im Rahmen einer konkreten Kernempfehlung.

Kernaussage ⇩	EVK ⇩	EMK ⇩	Leitlinie						
			ACP	AKDÄ	CPA	CTF	ICSI	NICE	NZGG
Pharmakotherapie – Antidepressiva allgemein (KE sieheTabelle 12)									
Therapieresistente / Chronische Depression Patienten mit therapieresistenter bzw. chronischer Depression sollte eine Kombination von Verhaltenstherapie und Antidepressiva angeboten werden	-	⇧-⇧⇧	-	-	-	-	☑	✓	-
Bei nur teilweisem Ansprechen auf ein Antidepressivum nach 3-4 Wochen sollte die Dosis erhöht werden. Bei Nichtansprechen / unzureichendem Ansprechen nach 4-8 Wochen: Dosiserhöhung / Wechsel des Antidepressivum, ergänzende / veränderte Psychotherapie, ggf. Überweisung an den Facharzt.	⇧ -	- ⇔-⇧⇧	✓ ✓	- -	- -	- -	- -	- ✓	- ✓
Pharmakotherapie – selektive Serotonin-Rückaufnahme-Inhibitoren (SSRI) (KE siehe Tabelle 13)									
Zur Behandlung akuter depressiver Episoden sind SSRI als Mittel der ersten Wahl empfohlen und in der Wirksamkeit den Trizyklika (TZA) gleichwertig.	⇧⇧	- ⇧-⇧⇧	- -	✓ -	✓ -	- -	☑	- ✓	- ✓
SSRI sind im Vergleich zu TZA zu bevorzugen, da sie weniger Nebenwirkungen haben und weniger Therapieabbrüche beobachtet wurden.	-	⇧⇧	-	☑	-	-	☑	✓	✓
Bei Patienten mit kardiovaskulären Erkrankungen ist Sertralin das Mittel der Wahl.	-	⇧	-	-	-	-	-	✓	-
Mittelschwere bis schwere Depression Bei Auftreten von erhöhter Agitation, Unruhe, Angstzuständen, Suizidgedanken sollte die Medikation überprüft werden (Wechsel des Antidepressivums, kurzfristige Benzodiazepin-Komedikation oder bei Wirkungslosigkeit ggf. zweites SSRI). Ein aktives und regelmäßiges Monitoring ist unerlässlich.	-	⇔	-	-	-	-	-	✓	☑
Atypische Depression Patienten mit atypischen Depressionen sollten mit SSRI behandelt werden. Bei Nichtansprechen ist eine Überweisung an einen Facharzt indiziert.	-	⇔	-	-	-	-	-	✓	☑

EVK: Evidenzkategorie; EMK: Empfehlungskategorie; KE: Kernempfehlung

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Kernaussage ⇩	EVK ⇩	EMK ⇩	Leitlinie						
			ACP	AKDÄ	CPA	CTF	ICSI	NICE	NZGG
Pharmakotherapie-Monoaminoxidase-Inhibitoren (MAO-Inhibitoren) (KE siehe Tabelle 14)									
Moclobemid, ein reversibler MAO-Inhibitor vom Typ A, ist gleich antidepressiv wirksam wie SSRI und TZA.	⇧⇧	-	-	✓	-	-	-	-	-
Bei Wechsel auf Moclobemid muss die vorherige Medikation ausgeschlichen werden.	-	⇧⇧	-	-	-	-	-	✓	-
Atypische Depression Phenelzin (Monitoring, Gefahr der Toxizität bei Überdosierung) sollte bei Frauen mit atypischer Depression erwogen werden, wenn sie SSRI nicht vertragen. Ein engmaschiges Monitoring (regelmäßige Blutdruckmessung) sowie Informierung des Patienten hinsichtlich potenzieller Interaktionen sollte erfolgen.	-	⇔	-	-	-	-	-	✓	-
Pharmakotherapie – nichtselektive Monoamin-Rückaufnahme-Inhibitoren (NSMRI) / Trizyklika (TZA) (KE siehe Tabelle 15)									
TZA sind bei akuten Depressionen wirksam.	⇧⇧	-	-	✓	-	-	-	-	-
TZA werden bei Patienten mit melancholischer Depression empfohlen.	-	⇔	-	-	-	-	-	-	✓
Die geringere Verträglichkeit von TZA im Vergleich zu SSRI ist zu beachten (insbesondere Kardiotoxizität und Toxizität bei Überdosierung / Suizidalität, hohes Interaktionspotenzial).	-	⇧	-	☑	-	-	☑	✓	-
TZA sollten nicht eingesetzt werden bei hohem Risiko für Herzrythmusstörungen und vor Kurzem erlittenem Herzinfarkt.	-	⇔	-	-	-	-	-	✓	-
Imipramin wird von Frauen weniger gut vertragen.	-	⇧	-	-	-	-	-	✓	-

EVK: Evidenzkategorie; EMK: Empfehlungskategorie; KE: Kernempfehlung

✓ Die Leitlinie unterstützt die Kernaussage im Rahmen einer konkreten Kernempfehlung.

☑ Die Leitlinie unterstützt die Kernaussage im Hintergrundtext, jedoch nicht im Rahmen einer konkreten Kernempfehlung.

Kernaussage ⇩	EVK ⇩	EMK ⇩	Leitlinie ACP	AKDÄ	CPA	CTF	ICSI	NICE	NZGG
Pharmakotherapie – weitere Antidepressiva (Selektive Serotonin- und Noradrenalin-Rückaufnahme-Inhibitoren [SSNRI] u. a.[1], Kombinations- / Augmentationstherapien (KE siehe Tabelle 16)									
Neue Antidepressiva[1] sind ähnlich gut wirksam wie SSRI und TZA.	⇧⇧	-	☑	✓	-	-	-	-	-
Aufgrund vergleichbarer Wirksamkeit sollten Antidepressiva der zweiten Generation[2] unter Abwägung von Nebenwirkungen, Kosten und Patientenpräferenzen ausgewählt werden.	⇧ -	- ⇧⇧	✓ ✓	- -	- -	- -	- -	- -	- -
Reboxetin: Überwachung ist wegen fehlender Daten zu Nebenwirkungen wichtig.	-	⇧	-	-	-	-	-	✓	-
Mirtazapin: Sedierende Wirkung und eine mögliche Gewichtszunahme sind zu berücksichtigen.	-	⇧⇧	-	☑	-	-	-	✓	-
Venlafaxin: Eine höhere nebenwirkungsbedingte Therapieabbruchwahrscheinlichkeit im Vergleich zu gleich wirksamen Antidepressiva ist zu beachten. Nebenwirkungen auf das Herz-Kreislaufsystem und eine geringere Überdosierungssicherheit / höheres Suizidalitätsrisiko im Vergleich zu SSRI (insbesondere bei jungen Erwachsenen) sind zu berücksichtigen.	-	⇧	-	-	-	-	-	✓	-
Venlafaxin sollte nicht eingesetzt werden bei hohem Risiko für Herzrhythmusstörungen, vor Kurzem erlittenem Herzinfarkt oder unkontrolliertem Bluthochdruck.	-	⇔	-	-	-	-	-	✓	-
Psychotische Depression Psychotische Patienten sollten neben Antidepressiva auch antipsychotische Medikamente einnehmen. Behandlungsdauer und Dosierung sind noch unbekannt.	-	⇔	-	-	-	-	-	✓	-

EVK: Evidenzkategorie; EMK: Empfehlungskategorie; KE: Kernempfehlung

✓ Die Leitlinie unterstützt die Kernaussage im Rahmen einer konkreten Kernempfehlung.

☑ Die Leitlinie unterstützt die Kernaussage im Hintergrundtext, jedoch nicht im Rahmen einer konkreten Kernempfehlung.

1: Venlafaxin / Duloxetin (SSNRI); Mirtazapin / Mianserin (Alpha2-Adrenozeptor-Antagonisten); Reboxetin (Selektiver Noradrenalin-Rückaufnahme-Inhibitor [SNRI])

2: Einschließlich Bupropion, Citalopram, Duloxetin, Escitalopram, Fluoxetin, Fluvoxamin, Mirtazapin, Nefazodon, Paroxetin, Sertralin, Trazodon, Venlafaxin.

Kernaussage ⇩	EVK ⇩	EMK ⇩	Leitlinie						
			ACP	AKDÄ	CPA	CTF	ICSI	NICE	NZGG
Pharmakotherapie – weitere Antidepressiva (Selektive Serotonin- und Noradrenalin-Rückaufnahme-Inhibitoren [SSNRI] u. a.[1], Kombinations- / Augmentationstherapien (KE siehe Tabelle 16)									
Bei therapieresistenter Depression kann unter Beachtung der Neben- und Wechselwirkungen ein zweites Antidepressivum (auch gleiche Klasse) verordnet werden (z. B. Mianserin / Mirtazapin in Ergänzung zu einem SSRI).	⇳ - ⇧ ⇧ -	- ⇳	- -	☑	- -	- -	✓ -	- ✓	- -
Als zweites Antidepressivum eignen sich SSRI oder Mirtazapin / Mianserin, aber auch Weitere (z. B. Moclobemid, Reboxetin) oder TZA. Venlafaxin kann bei schwereren Depressionen eingesetzt werden.	-	⇳	-	-	-	-	-	✓	☑
Bei Patienten, die auf verschiedene Antidepressiva nicht angesprochen haben, sollte eine Augmentationsbehandlung mit Lithium erwogen werden (EKG durchführen).	⇳ - ⇧ ⇧ -	- ⇧	- -	☑	- -	- -	✓ -	- ✓	- -
Bei Kombinations- / Augmentationstherapien sollte ein engmaschiges Monitoring erfolgen (z. B. Gefahr eines Serotoninsyndroms, bei Phenelzin / Venlafaxin: Gefahr der Toxizität bei Überdosierung, bei Mianserin: Gefahr einer Agranulocytose)	-	⇳	-	-	-	-	-	✓	-
Andere Kombinationen von Antidepressiva als die o. g. sollten vor Verschreibung mit einem Kollegen diskutiert werden.	-	⇳	-	-	-	-	-	✓	-
Eine Kombination mit Carbamazepin, Lamotrigin, Buspiron, Pindolol, Valproat oder Schilddrüsenhormonen ist in der Routineversorgung der therapieresistenten Depression nicht zu empfehlen.	-	⇧	-	☑	-	-	-	✓	-
Dosulepin und Benzodiazepine werden zur Verstärkung von Antidepressiva nicht empfohlen.	-	⇳	-	-	-	-	-	✓	-

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1: Venlafaxin / Duloxetin (SSNRI); Mirtazapin / Mianserin (Alpha2-Adrenozeptor-Antagonisten); Reboxetin (Selektiver Noradrenalin-Rückaufnahme-Inhibitor [SNRI])

Kernaussage ⇩	EVK ⇩	EMK ⇩	Leitlinie						
			ACP	AKDÄ	CPA	CTF	ICSI	NICE	NZGG
Pharmakotherapie – Phytotherapeutika (KE siehe Tabelle 17)									
Leichte bis mittelschwere Depression Johanniskraut ist im Vergleich zu Placebo bei leichten bis mittelschweren Depressionen wirksam.	⇧⇧	-	-	✓	-	-	-	-	☑
Johanniskraut sollte wegen möglicher schwerwiegender Medikamenten-interaktionen nicht verordnet werden. Patienten sollten über potenzielle Interaktionen mit Kontrazeptiva, Antikoagulanzien und krampflösenden Medikamenten aufgeklärt werden.	-	⇔	-	☑	-	-	-	✓	-
Mittelschwere bis schwere Depression Johanniskraut ist bei mittelschwerer bis schwerer Depression nicht wirksamer als Placebo und sollte nicht verordnet werden.	⇔ -	- ⇔	- -	✓ -	- -	- -	- -	- ✓	- -

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Kernaussage ⇩	EVK ⇩	EMK ⇩	Leitlinie						
			ACP	AKDÄ	CPA	CTF	ICSI	NICE	NZGG
Pharmakotherapie – Erhaltungstherapie / Rezidivprophylaxe (KE siehe Tabelle 18)									
Die Remissionserhaltung nach erfolgreicher Akuttherapie sollte mit dem eingesetzten Antidepressivum in unveränderter Dosierung über 6 Monate fortgesetzt werden (auch wenn in Kombinationstherapie mit Lithium).	⇔-⇧ -	- ⇧-⇧⇧	✓ ✓	☑	- -	- -	✓ -	- ✓	- ✓
Die Rezidivprophylaxe ist für SSRI / TZA bei unipolaren Depressionen gut belegt.	⇧⇧	-	-	✓	-	-	-	-	-
Eine regelmäßige Überprüfung der Therapie wird empfohlen.	-	⇔-⇧	-	-	-	-	-	✓	✓
Für uni- und bipolare Depressionen ist die Wirksamkeit einer Prophylaxe mit Lithium eindeutig belegt. Lithium ist Amitriptylin überlegen.	⇧⇧	-	-	✓	-	-	-	-	-
Lithium sollte zur Verhinderung einer rezidivierenden Depression nicht allein gegeben werden.	-	⇔	-	-	-	-	-	✓	-
Bei unzureichendem Ansprechen auf Lithium oder bei Unverträglichkeit ist Carbamazepin Mittel der (zweiten) Wahl.	⇧	-	-	✓	-	-	-	-	-
Zur Remissionsstabilisierung mit Johanniskraut kann aufgrund mangelnder Kernempfehlungen keine Kernaussage formuliert werden.	⇔	-	-	✓	-	-	-	-	-
Andere Antikonvulsiva werden zur Rezidivprophylaxe nicht empfohlen.	⇔	-	-	✓	-	-	-	-	-
Patienten mit wiederholten depressiven Episoden sollten 2 Jahre die antidepressive Therapie fortsetzen, und zwar in der im Rahmen der Remission bewährten Dosis.	-	⇧	☑	-	-	-	-	✓	☑
Über den Zeitrahmen von 2 Jahren hinaus sollte die Therapienotwendigkeit unter Beachtung von Alter, Komorbidität und anderer Risikofaktoren überprüft werden.	-	⇔	-	-	-	-	-	✓	-

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Kernaussage ⇩	EVK ⇩	EMK ⇩	Leitlinie						
			ACP	AKDÄ	CPA	CTF	ICSI	NICE	NZGG
Nichtmedikamentöse Therapie – Psychotherapie / Psychosoziale Intervention (KE siehe Tabelle 20)									
Leichte bis mittelschwere Depression Eine alleinige psychotherapeutische / psychosoziale Behandlung (unterstützende Gespräche, Selbstmanagement, Problemlösungstherapie, kognitive Verhaltens-therapie u. a.) kann bei leichter bis mittelschwerer Depression versucht werden (6-8 Sitzungen über 10-12 Wochen)	-	⇳	-	☑	-	-	☑	✓	✓
„Hilfe zur Selbsthilfe" basierend auf der kognitiven Verhaltenstherapie wird empfohlen.	-	⇧	-	-	-	-	-	✓	-
Mittelschwere bis schwere, chronische / therapieresistente Depression Zusätzlich zur pharmakologischen Therapie stehen evidenzbasierte psychotherapeutische / psychosoziale Interventionen zur Verfügung.	-	⇧	-	☑	-	-	☑	✓	✓
Die Psychotherapie der ersten Wahl ist die kognitive Verhaltenstherapie (CBT). Gegebenenfalls kann die Interpersonelle Therapie versucht werden. (16-18 Sitzungen über 6-9 Monate)	-	⇧	-	-	-	-	☑	✓	✓
Eine Kombinationstherapie mit Pharmako- und Psychotherapie sollte bei Erstdiagnose einer schweren Depression sowie bei chronischer, sehr schwerer oder therapieresistenter Depression erfolgen.	-	⇧	-	☑	-	-	-	✓	✓
Eine Paartherapie sollte bei depressiven Patienten erwogen werden, die einen Lebenspartner haben und von einer Individualtherapie nicht profitiert haben.	-	⇧	-	-	-	-	-	✓	-

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Kernaussage ⇩	EVK ⇩	EMK ⇩	Leitlinie						
			ACP	AKDÄ	CPA	CTF	ICSI	NICE	NZGG
Nichtmedikamentöse Therapie – Psychotherapie / Psychosoziale Intervention (KE siehe Tabelle 20)									
Eine kognitive Verhaltenstherapie sollte z. B. dann alleinig eingesetzt werden, wenn Patienten eine Behandlung mit Antidepressiva oder Behandlungsalternativen									
▪ nicht durchführen können oder wollen (z. B. aufgrund von Nebenwirkungen),	-	⇧	-	-	-	-	-	✓	-
▪ andere Maßnahmen (Antidepressiva, CBT u. a.) keine angemessene Wirkung zeigen,	-	⇔	-	-	-	-	-	✓	-
▪ nicht durchführen können oder wollen, aber eine Erhaltungstherapie aufgrund eines erhöhten Rückfallrisikos notwendig erscheint.	-	⇧	-	-	-	-	-	✓	-
Die achtsamkeitsbasierte kognitive Therapie (normalerweise in Gruppentherapie) sollte bei Patienten erwogen werden, die schon 3 oder mehr Depressionsepisoden durchlebt haben (Rezidivprophylaxe).	-	⇧	-	-	-	-	-	✓	-
Nichtmedikamentöse Therapie – weitere nichtmedikamentöse Interventionen (KE siehe Tabelle 20)									
Leichte Depression									
▪ Schlaf- und Angstmanagement, „Watchful Waiting", Bewegungstherapie	⇔ -	- ⇔	- -	☑	- -	- -	✓ -	- ✓	☑
▪ Lichttherapie bei leichter bis mittelgradig rezidivierender Depression mit saisonalen Einflüssen	⇔-⇧⇧	-	-	☑	-	-	✓	-	-

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Kernaussage ⇩	EVK ⇩	EMK ⇩	Leitlinie						
			ACP	AKDÄ	CPA	CTF	ICSI	NICE	NZGG
Nichtmedikamentöse Therapie – weitere Nichtmedikamentöse Interventionen (KE siehe Tabelle 20)									
Schwere Depression Elektrokrampftherapie (EKT): EKT sollte bei Patienten mit schwerer Depression nur dann erwogen werden, wenn eine schnelle und kurzfristige Besserung einer schweren Symptomatik angestrebt wird, die durch andere Behandlungsoptionen nicht erreicht werden kann / konnte oder die einen lebensbedrohlichen Zustand auslöst / ausgelöst hat. (Einschränkungen siehe KE)	-	⇔	-	-	-	-	-	✓	-
EKT kann u. a. bei resistenter Depression, schwerer psychischer Beeinträchtigung, akuter Suizidalität und psychotischen Symptomen erwogen werden.	⇧	-	-	☑	-	-	✓	-	-
Chronische Depression Wenn die Depression über einen längeren Zeitraum zum Verlust der Arbeitsstelle oder zum Rückzug von anderen sozialen Aktivitäten geführt hat, sollte ein entsprechendes Rehabilitationsprogramm erwogen werden.	-	⇔	-	-	-	-	-	✓	-

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Anlage 2: Hauptunterschiede in spezifischen Nebenwirkungen

Drug	Comparators	Differences in Adverse Events
Bupropion	Escitalopram, fluoxetine, paroxetine, sertraline	Lower incidence of sexual dysfunction than comparator drugs (6% vs. 16%)
Mirtazapine	Fluoxetine, paroxetine, trazodone, venlafaxine	Greater weight gain than comparator drugs (mean, 0.8–3.0 kg after 6–8 wk)
Paroxetine	Escitalopram, duloxetine, fluoxetine, mirtazapine, nefazodone, and sertraline	Higher incidence of sexual dysfunction, particularly ejaculatory dysfunction, than comparator drugs
Sertraline	Bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, venlafaxine	Higher incidence of diarrhea than comparator drugs (mean, 16% [95% CI, 13%–20%] vs. 8% [CI, 4%–13%])
Trazodone	Bupropion, fluoxetine, mirtazapine, paroxetine, venlafaxine	Higher incidence of somnolence than comparator drugs (mean, 42% [CI, 19%–64% vs. 25% [CI, 3%–46%])
Venlafaxine	SSRIs as a class	Higher incidence of nausea and vomiting than SSRIs as a class (mean, 33% [CI, 23%–43%] vs. 22% [CI, 16%–29%])