**Figure S1.** Search strategy used for each database

Limits: English, Humans, all adults (19 +), published from inception to December 2021.

1. (stage AND psychiatric disorder) OR staging AND psychiatric disorder
2. (stage AND mental disorder) OR staging AND mental disorder
3. (stage AND mood disorder) OR staging AND mood disorder
4. (stage AND depressive) OR staging AND depressive

**Figure S2.** Flow diagram of the search

Identification of new studies via citation searching

Identification of new studies via databases

Records identified from:

* EMBASE (n = 101,618)
* PubMed (n = 37,338)
* Web of Science (n = 19,409)
* PsycINFO (n = 4,894)

Duplicate records removed before screening

(n = 32,651)

Records identified

(n = 137)

Records screened

(n = 130,608)

Records excluded

(n = 130,253)

Reports not retrieved

(n = 0)

Reports sought

for retrivial (n = 325)

Reports sought

for retrivial (n = 34)

Reports not retrieved

(n = 0)

Reports excluded

(n = 168) for:

* 77 off topic
* 59 no original data/models
* 13 studies with data published also in other studies
* 6 including not only adults
* 8 sample < 10 subjects
* 3 no DSM or ICD diagnoses
* 2 special populations

Reports excluded

(n = 22) for:

* 9 no original data/models
* 8 studies with data published also in other studies
* 3 including not only adults
* 1 no DSM or ICD diagnoses
* 1 transdiagnostic

Reports assessed for eligibility (n = 325)

Reports assessed for eligibility (n = 34)

Reports of new included studies (n = 169):

* on staging models or their use (n = 18)
* on treatment-resistant staging models or their use (n = 151)

**Table S1.** Staging models of longitudinal development of unipolar depression and their applications: data extracted from study documents

|  |
| --- |
| **STAGING MODELS OF LONGIDUTINAL DEVELOPMENT OF UNIPOLAR DEPRESSION** |
| **Authors and date** | **Setting** | **Population** | **Design** | **Model**  |
| Fava & Kellner, 1993 | Review  |  |  | Stage 1: prodromal, with deterioration of functioningStage 2: acute episode Stage 3: residual Stage 4: subchronic (< 2 yrs but > 6 months)Stage 5: chronic (> 2 yrs) |
| McGorry et al., 2006 | Review  |  |  | Stage 0: Increased risk of severe mood disorder, no current symptomsStage 1a: Mild or non-specific symptoms. Mild functional change or declineStage 1b (Ultra high risk): moderate subthreshold symptoms, withmoderate neurocognitive changesand functional decline to casenessStage 2: first episode of severe mood disorder withmoderate-severe symptoms,neurocognitive deficits and functional declineStage 3a: incomplete remission Stage 3b: Recurrence or relapse which stabilizes with treatment at a level below the best levelachieved following remission fromfirst episodeStage 3c: multiple relapses, providedworsening in clinical extent Stage 4: severe, persistent or unremitting illness |
| Fava & Tossani, 2007 | Review  |  |  | 1. Prodromal phase a. No depressive symptomsb. Minor depression2. Major depressive episode3. Residual phasea. No depressive symptomsb. Dysthymia4. a. Recurrent depressionb. Double depression5. Chronic major depressive episode (at least 2 years) |
| Hetrick et al., 2008 | Review  |  |  | Modified from McGorry et al., 2006:Stage 0: increased risk of anxiety or depressive disorder; no symptoms currentlyStage 1a: mild or nonspecific symptoms of anxiety or depression, including neurocognitive deficits of severe mood disorder; mild functional change or declineStage 1b (ultra-high risk): moderate but sub-threshold symptoms of anxiety or depression, with moderate neurocognitive changes and functional decline to casenessStage 2: first episode of major depressive disorder; full-threshold disorder with moderate to severe symptoms, neurocognitive deficits and functional declineStage 3a: incomplete remission from first episode of careStage 3b: recurrence or relapse of depressive disorder which stabilizes with treatment at the level of residual symptoms or neurocognition below the best level achieved following remission from first episodeStage 3c: multiple relapses, provided worsening in clinical extent and impact of illness is objectively presentStage 4: severe, persistent or unremitted illness |
| Cosci & Fava, 2013 | Systematic review |  |  | Stage 1: Prodromal phase* No depressive symptoms with mild functional change or decline
* Mood symptoms (sad mood, subsyndromal depression)

Stage 2: MDEStage 3: Residual phase* No depressive symptoms
* Mood symptoms
* Dysthymia

Stage 4:* Recurrent depression
* Double depression

Stage 5:Chronic major depressive episode |
| Boschloo et al., 2014 | Netherlands Study of Depressionand Anxiety  | 767 patients with DSM-IV MDD.Patients who had been mildly depressed for at least 24 months were defined chronically depressed at baseline | Prospective comparative cohort trial | The following groups were identified: (1) sustained recovery (with or without residual symptoms): no major depressive disorder at follow-up (2) temporary recovery (with or without residual symptoms): major depressive disorder during follow-up(3) chronic course: major depressive disorder during follow-up and at least mild depressive symptoms for 24 months or more |
| Ferensztajn et al., 2014 | Review |  |  | Modified from Fava & Kellner, 1993:Stage 1 (prodromal phase): risk factors without depressive symptoms (stage 1a) or with subdepres­sive symptoms, not achieving severity of the depressive episode (stage 1b)Stage 2: first episode of depression Stage 3: residual phase with full remission (stage 3a) or dysthymia (stage 3b)Stage 4: recurrence (stage 4a) or double depression (stage 4b) Stage 5: chronic course of illness (over two years)  |
| Wardenaar et al., 2015 | in primary care | 205 patients with DSM-IV MDD | Prospective comparative cohort trial | Four classes: quick recovery, persisting somatic symptoms, persisting mood/cognitive symptoms, persisting both somatic symptoms and mood/cognitive symptoms (chronic) |
| Verhoeven et al., 2018 | patients recruited from 49 Dutch general practices | 213 patients with ICD current, or recent MDE | Prospective comparative cohort trial | Slow symptomdecline: declining residual symptoms until week 24 Quick symptom decline: persistent low symptomratings over the whole 24-week period Steady residual symptoms: persisting residual levels ofsymptomatology during the whole 24-week period Slow symptom increase: a course trajectory of increasing symptomatology |
| Nelson et al., 2021 | Position paper |  |  | Stage 0: asymptomatic.Stage 1a: distress disorder.Stage 1b Distress disorder and subthreshold specificity.Stage 2 First treated episode Stage 3 Recurrence or persistence Stage 4 Treatment resistance. |
| **APPLICATIONS** |
| **Authors and date** | **Setting** | **Population** | **Design** | **Main results** |
| Fava et al., 1994 | Affective Disorders Program, University of Bologna School of Medicine  | 40 DSM-IIIR depressed outpatients in stage 3 of unipolar depression according to Fava & Kellner (1993) staging model  | Randomized clinical trial with follow-up | When the residual symptoms of those who received cognitive behavioral therapy and those who received clinical management were compared, a significant effect of cognitive behavioral treatment was found (F=23.89, df=1, p<0.0001)  |
| Fava et al., 1998a | Affective Disorders Program, University of Bologna School of Medicine | 40 RDC depressed outpatients in stage 3 of unipolar depression according to Fava & Kellner (1993) staging model who were tested in Fava et al., 1994 were here re-assessed | Randomized clinical trial with follow-up | Patientsin the cognitive behavioral treatment group had a significantly lower number of new depressive episodes(mean=0.80; SD=0.95) than those in the standard clinical management group (mean=1.70, SD= 1.30) (t=2.50, df=38, p<0.05) |
| Fava et al., 1998b | Affective Disorders Program, University of Bologna School of Medicine | 40 RDC depressed outpatients in stage 3 of unipolar depression according to Fava & Kellner (1993) staging model | Randomized clinical trial with follow-up | When the residual symptoms of those who received cognitive behavioral therapy and those who received clinical management were compared a significant effect of cognitive behavioral treatment was found (F=31.54, df=1,37, p<0.001) |
| Fava et al., 1998c | Consecutive out-patients referred to the Affective DisordersProgram, University of Bologna School ofMedicine | 20 patients with currentDSM-IV MDD orpanic disorder at stage 3 according to Fava & Kellner (1993) | Randomized clinical trial with follow-up  | Both well-being therapy andCognitive behavioural therapy were associatedwith decrease in residual symptoms. After well-being therapy andcognitive behavioural treatment, significant effect of wellbeing therapy (t=5.58; df=18; p<0.001) was found |
| Verduijn et al., 2015a | Netherlands Study of Depressionand Anxiety | 2,333 subjects with DSM-IV MDD | Prospective comparative cohort trial | Hetrick et al. (2008) staging model was tested for construct and predictive validity. Severity, duration, disability scored progressively worse over stages 0 to 4, suggesting construct validity. Predictive validity was poor when the model’s performance was considered in predicting 2 years follow-up outcomes |
| Verduijn et al., 2015b | Netherlands Study of Depressionand Anxiety  | 2,563 subjects who were either health controls (n = 230) or assigned to one of the eight stages of major depressive disorder according to Hetrick et al. (2008). Diagnosis was formulated according to DSM-IV | Prospective comparative cohort trial | Hetrick et al. (2008) staging model was used.Three (inflammation, HPA-axis and vitamin D) mechanisms showed increasing trends of dysregulation across healthy controls and the at-risk stages (0, 1A and 1B) of depression, but not across the full-threshold stages (2, 3A, 3B, 3C and 4) |
| Reneses et al., 2020 | Outpatients from four Community Mental Health Care Centres of the Department of Psychiatry & Mental Health at the San Carlos University Hospital in Madrid | 133 subjects with ICD-10 depressive disorder with a current episode according to Hetrick et al. (2008)  | Cross-sectional study | The most frequent stage was 3b1 (38.3%), followed by stage 2 (21.8%) and stage 3b2 (17.3%). The less frequent stages were stage 3c (7.5%) and stage 4 (5.3%).Differences between clinical stages in resistance to treatment (measured by the Maudsley Staging Method) were statistically significant between the following pairs of stages: 2 and 3b2 (p = 0.026); 2 and 3c (p = 0.20); 2 and 4 (p = 0.002; 3b1 and 3b2 (p = 0.025); 3b1 and 3c (p = 0.026); 3b1 and 4 (p = 0.002) |

MDD: Major depressive Disorder; MDE: Major Depressive Episode; N/A: Not Applicable

**Table S2a.** Treatment-resistance unipolar depression staging models: data extracted from study documents

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Authors and date** | **Setting** | **Population** | **Design** | **Model proposed** |
| Thase and Rush, 1997 | Review |  |  | Stage I: failure of at least one adequate trial of antidepressantsStage II: Stage I resistance plus failure of an adequate trial of an antidepressant in a distinctly different class Stage III: Stage II resistance plus failure of an adequate trial of a TCAStage IV: Stage III resistance plus failure of an adequate trial of a MAOIStage V: Stage IV resistance plus failure of a course of bilateral ECT |
| Souery et al., 1999 | Review |  |  | The European Staging MethodResistance: Major depression with lack of response to an adequate antidepressant trial.1. Non Responder to TCA, SSRI, MAOI, SNRI, ECT, other; – Non response to one adequate antidepressant trial; – Duration of trial: 6–8 weeks.
2. TRD

–Resistance to 2 or more adequate antidepressant trials– Duration of trial(s): TRD 1: 12–16 weeksTRD2: 18–24 weeksTRD3: 24–32 weeksTRD4: 30–40 weeksTRD5: 36 weeks–1 year1. CRD

– Resistance to several antidepressant trials, including augmentation strategy. - Duration of  trial(s):  at least 12 months |
| Corey-Lisle et al., 2002 | Review plus data derived from employer administrative files | 4,186 patients with a medical and disability claim from ICD-9 MDD | Prospective comparative cohort trial | Treatment-Resistant Depression Scale Criteria:Dimension I: treatment with an antidepressant and mood stabilizer/treatment with an antidepressant and an atypical antipsychotic (maximum score 2).Dimension II: switching (score 0-3).Dimension III: titration (score 0-3).A cut-off of 5 allowed to identify TRD likely patients |
| Fava, 2003 | Review  |  |  | Massachusetts General Hospital Staging Method1) Nonresponse to each adequate (at least 6 weeks of an adequate dose of antidepressant) trial of an antidepressant (1 point per trial)(2) Optimization of dose, optimization of duration, and augmentation/combination of each trial increase the overall score (0.5 point per trial per optimization/strategy)(3) ECT increases the overall score by 3 points |
| Fekadu et al., 2009a | Review |  |  | Maudsley Staging MethodDuration* acute (≤ 12 months) (score1)
* sub-acute (13-24 months) (score 2)
* chronic (> 24 months) (score 3)

Symptom severity (baseline)* subsyndromal (Score 1)
* syndromal

mild (score 2)moderate (score 3)severe without psychosis (score 4)severe without psychosis (score 5)Treatment failure antidepressantsLevel 1: 1-2 medications (score 1)Level 2: 3-4 medications (score 2)Level 3: 5-6 medications (score 3)Level 4: 7-10 medications (score 4)Level 5: > 10 medications (score 5)Augmentation* not used (score 0)
* used (score 1)

Electroconvulsive therapy* not used (score 0)
* used (score 1)

All factors in the model independently predicted resistance at discharge. The final model correctly predicted treatment resistance in 85.5% of cases (linear trend χ2 16.12, p < 0.001) while the Thase and Rush model was less predictive (linear trend χ2 6.14, p < 0.013) |
| Cosci & Fava, 2013 | Systematic review |  |  | Stage 0: no history of failure to therapeutic trial.Stage 1: failure of at least one adequate therapeutic trial. Duration of trial: 6–8 weeks.Stage 2: failure of at least two adequate therapeutic trials.Duration of each trial from 12–16 weeks to 36 weeks–1 year.Stage 3: failure at least three therapeutic trials.Duration of each trial lasting from 12–16 weeks to 36 weeks–1 year.Stage 4: failure of three or more adequate trials including at least one concerned with augmentation/combination or electroconvulsive therapy. Duration of each trial at least 3 months. |
| Conway et al., 2017 | Position paper |  |  | Stage I: failure of 2 adequate dose-duration antidepressants or psychotherapy from different classes (either in combination or succession) in the current episode.Stage II: failure of 3 or more adequate antidepressant or psychotherapy trialsfrom different classes (either in combination or succession) in thecurrent episode |

TCA: tricyclics; SSRI: Selective Serotonin Reuptake Inhibitors; MAOI: Monoamine Oxidase Inhibitors; SNRI: Selective Noradrenaline Reuptake Inhibitors; ECT: Electroconvulsive Therapy; TRD: Treatment-Resistant Depression; CHRD: Chronic-Resistant Depression; MDD: Major Depressive Disorder; rTMS: repetitive Transcranial Magnetic Stimulation; N/A: Not Applicable

**Table S2b.** Applications of treatment-resistance depression staging models: data extracted from study documents

|  |
| --- |
| **THASE AND RUSH (1997)** |
| **Authors and date** | **Setting** | **Population** | **Design** | **Main results** |
| Bocchio-Chiavetto et al., 2006 | Villa S. Chiara Private Clinic Verona | 23 patients with ICD-10 Major Depression at stage III according to Thase and Rush (1997) | Prospective longitudinal | A significant increase of BDNF was found over the time [(G—G) correction: F(1.96, 43.05) = 7.64; p = 0.002] |
| Fitzgerald et al., 2006a | inpatients across 3 hospital sites | 130 patients with DSM-IV MDD at Stage II according to Thase and Rush(1997) | Case-control study with follow-up | no difference between 1- or 2-Hz rTMS |
| Fitzgerald et al., 2006b | outpatient department of a public regional mental health service and private psychiatrists | 50 patients with DSM-IV MDD at Stage II according to Thase and Rush(1997) | Randomized clinical trial | A significant proportion of subjects receiving rTMS met response (44%) or remission (36%) compared to the sham group(8% or 0%, respectively) |
| Bares et al., 2007 | Inpatients at the Prague Psychiatric Centre, Prague | 17 patients with DSM-IV MDD at least at Stage I according to Thase and Rush (1997) | Single-arm study | The subjects were treated with various antidepressants.Responders andNon responders differed in prefrontal cordance changes both in week 1 and week 4 (U = 2.0; p = 0.001 resp. U = 10.0; p = 0.04) |
| Kito et al., 2008 | Kyorin University School of Medicine | 14 patients with DSM-IV MDD at Stage II or III according to the Thase and Rush (1997) | Case-control study with follow-up | As compared with nonresponders, responders showed significant increasesin regional cerebral blood flow at baseline in the left hemisphere including the prefrontal and limbic-paralimbic regions |
| Baeken et al., 2009 | Medication-freepatients | 23 patients with DSM-IV unipolar depression melancholic subtype at least at Stage III according to Thase and Rush (1997)  | Cross-sectional study | The difference (median) in salivary cortisol concentrations between T1 and T2 after real and sham High Frequency rTMS was −0.80 (IR=2.65 μg/L) (p=0.03) |
| Bares et al., 2009 | Inpatients at the Prague Psychiatric Centre | 60 patients with DSM-IV MDD at least at Stage I according to Thase and Rush (1997) | Randomized controlled trial | Patients were randomly assigned to 1 Hz rTMSwith placebo and venlafaxine with sham rTMS for 4 weeks.No significant differences between 1 Hz rTMS plus placebo or venlafaxine plus sham rTMS were found in terms of depressive symptoms, response rates, remission, and dropouts |
| Fernandes et al., 2009 | InpatientPsychiatric Unit, Hospital de Clinicas de Porto Alegre | 15 patients with DSM-IV MDD at Stage III according to Thase and Rush (1997) | Single-arm study with follow-up | There were no changes in the serum BDNF before and after the ECT treatment |
| Fitzgerald et al., 2009 | Outpatients at the Alfred PsychiatryResearch Centre from the Alfred Department of Psychiatryand by referral from a number of private psychiatrists | 51 patients with DSM-IV MDD at Stage II according to Thase and Rush (1997) | Randomized clinical trial | The use of neuro-navigational methods to target a specific dorsolateral prefrontal cortex site enhanced response to rTMS |
| Siwek et al., 2009 | Patients at admission to the Department of Psychiatry Collegium Medicum Jagiellonian University or to Affective Disorder Outpatients  | 60 patients with DSM-IV MDD and treatment resistance according to Thase and Rush (1997) | Randomized clinical trial | No significant differences in depressive symptom severity were demonstratedbetween zinc-supplemented and placebo-supplemented antidepressant treatment nonresistant patients. Zinc supplementation significantly reduced depression scoresand facilitated the treatment outcome in antidepressant treatment resistant patients |
| Zhang et al., 2009 | Patients recommended for ECT  | 16 patients with DSM-IV MDD | Case-control study | Treatment resistance was assessed according to Thase and Rush (1997).When patients were sub-classified into ECT responders and non-responders, serum GDNF levels were significantly increased (58%) in responsive patients following ECT  |
| Bares et al., 2010 | Inpatients at the Center for Treatmentof Resistant Depression of Prague PsychiatricCenter | 81 patients with DSM-IV MDD at least at Stage I according to Thase and Rush (1997) | Retrospective cohort study | The group who received a combination of drugs achieved higher reduction of depressive symptoms (p = 0.02) and response rate (p = 0.03) than the group in monotherapy |
| Bonvicini et al., 2010 | Villa S. Chiara Private Clinic, Verona | 310 patients with DSM-IV severe MDD at Stage III according to Thase and Rush (1997) | Case-control study | The sequencing analysis showed that rs25531 is immediately outside of the 5-HTTLPR segment |
| Fang et al., 2010 | inpatient and outpatient services of 8 psychiatric hospitals across mainland China | 150 patients with DSM-IV MDD at Stage II according to Thase and Rush (1997) | Randomized clinical trial | There were no difference concerning remission rates for venlafaxine-XR, mirtazapine, and paroxetine |
| Kito et al., 2010 | Kyorin University School of Medicine | 20 patients with DSM-IV-TR MDD and treatment resistance according to Thase and Rush (1997) | Case-control study | There were no significant changes in fT3 and fT4 levels measuredat either pre- or post-low-frequency right prefrontal transcranial magneticstimulation in either responders or nonresponders. TSH levels of responders elevated significantly after transcranial magneticstimulation |
| Okazaki et al., 2010 | St. Marianna UniversitySchool of Medicine | 24 patients DSM-IV MDD bipolardisorder with current MDE at Stage III according to Thase and Rush (1997) | Case-control study | No significant difference was observed in depressive symptoms between responders and non-responders to ECT |
| Pallanti et al., 2010 | Outpatients at the Institute for Neurosciences | 60 patients with DSM-IV MDD at Stage II according to Thase and Rush (1997) | Randomized clinical trial | Only the unilateral rTMS was significantly more effective than sham at the end of the trialand correlated to the higher percent of remitters (30% of thegroup vs. 10% -bilateral- and 5% -sham) |
| Kito et al., 2011 | Kyorin University School of Medicine | 26 patients with DSM-IV-TR MDD and treatment resistance according to Thase and Rush (1997) | Single-arm study | Significant decreases in regional cerebral blood flow after low-frequency right prefrontal stimulation were seen in the prefrontal cortex, orbitofrontal cortex, subgenual cingulate cortex, globus pallidus, thalamus, anterior and posterior insula, midbrain in the right hemisphere |
| Barbee et al., 2011 | 19 sites | 180 patients with DSM-IV/ICD-10 unipolar depression  | Randomized clinical trial | Patients were staged according to Thase and Rush (1997).The primary a priori analysis did not differentiate between lamotrigine and placebo |
| Fitzgerald et al., 2011 | by referral from privatepsychiatrists | 219 patients with DSM-IV MDD at Stage II according to Thase and Rush (1997) | Randomized clinical trial | There was no substantialdifference in response between the unilateral and bilateral treatment groups |
| Malaguti et al., 2011 | inpatients consequently admitted tothe Research Centre for Mood Disorders, San Raffaele Hospital | 90 patients with DSM-IV MDD with treatment resistance according to Thase and Rush (1997) | Single-arm study | A significant model in which whereas factor 5-HT(1A) showed a significant influence on the outcome, with patients with C/C genotype showing a greater improvement than G/G and C/G and no difference between G/G and C/G |
| Minelli et al., 2011 | Villa S. Chiara Private Clinic | 19 patients with DSM-IV MDD at Stage III according to Thase and Rush (1997) | Single-arm study | No changesoccurred in serum VEGF between T0 and T1 of ECT treatment, a significant increase was observed between T0 and T2 (p=0.042) |
| Fitzgerald et al., 2012 | single site | 67 patients with DSM-IV MDD at Stage II according to Thase and Rush (1997) | Randomized clinical trial | Consistent pattern of improved response in unilateral left compared to bilateral rTMS |
| Hori and Kunugi, 2012 | outpatient clinic of theNCNP Hospital or from community | 17 patients with DSM-IV MDE with Stage II or III according to Thase and Rush (1997) | Single-arm study | 71% patients were responders, 59% remitted under pramipexole |
| Pallanti et al., 2012 | Outpatients  | 28 patients DSM-IV MDD at Stage II according to Thase and Rush (1997) | Single-arm study | At the end of low-frequency rTMS (1 Hz) over theright left dorsolateral prefrontal cortex, 42.9% of the subjects were considered responders |
| Richieri et al., 2012 | public psychiatric teaching hospital | 61 patients with DSM-IV MDD with treatment resistance according to Thase and Rush (1997) | Retrospective cohort study | rTMS efficiency was statistically equivalent when high frequency (10Hz) left-side stimulation was compared with low frequency (1Hz) right-side stimulation |
| Bauer et al., 2013 | 107 non-primary care sites in Australia, Austria, Belgium, Bulgaria, Germany, Hungary, Italy, Portugal, Romania, Slovakia, Spain, UK | 688 patients with DSM-IV MDD at Stage I or II according to Thase and Rush (1997) | Randomized clinical trial | At week 6, the differences between groups (i.e., add-on quetiapine XR and quetiapine XR monotherapy compared with add-on lithium) were similar |
| Bowie et al., 2013 | tertiary clinic in Kingston | 33 patients with DSM-IV current MDE and treatment resistance according to Thase and Rush (1997) | Randomized clinical trial | There was a significant time by treatment interaction for attention/processing speed and verbal memory |
| De Berardis et al., 2013 | Outpatients at mental health facilities in Central Italy | 25 with aDSM-IV MDD at Stage II according to Thase and Rush (1997) | Single-arm study | A significant decrease in depressive symptom severity was observed with response achieved by 60% of the patients and remission by 36% |
| Echizenya et al., 2013 | Consecutively admitted inpatients of Akita UniversityHospital  | 13 patients with DSM-IV MDE | Single-arm study | According to Thase and Rush (1997), no patients belonged to Stage I, 3 patients belonged to Stage II, 8 patients belonged to Stage III, 1patient belonged to Stage IV, 1 patient belongedto Stage V |
| Fitzgerald et al., 2013 | 4 private psychiatrichospitals in the Australian states of Victoria, NewSouth Wales and Queensland | 179 patients with DSM-IV MDD at Stage II according to Thase and Rush (1997) | Randomized clinical trial | There were no significant differences in clinical response between sequential bilateral rTMS and right-sided unilateral rTMS |
| Gupta et al., 2013 | Outpatients at Mood Disorders Research and Treatment Service at Providence Care Mental Health Services in Kingston | 33 patients with DSM-IV MDD at least at Stage I according to Thase and Rush (1997) | Descriptive study | Patients had mildly reduced performance across all neurocognitive domains with a superimposed moderate impairment in verbal working memory |
| Lin et al., 2013 | Inpatient Psychiatric Unit of Kai-Syuan Psychiatric Hospital | 55 patients with DSM-IV MDD or bipolar disorder with a current MDE with Stage II or III according to Thase and Rush (1997) | Single-arm study | The severity of depressionwas significantly reduced (p < 0.001) after ECT |
| Wu et al., 2013 | Optimized Treatment Strategies for Treatment-Resistant Depression conducted at 8 psychiatric sites across mainland China | 55 patients with DSM-IV MDD at Stage II according to Thase and Rush (1997) | Case-control study | Remission rates were significantly lower and ratings of adverse event frequency were significantly greater in patients with anxious treatment resistance than in those with non-anxious treatment resistance |
| Minelli et al., 2014 | Psychiatric RehabilitationUnit of IRCCS Centro S. Giovanni di Dio FBF,Mood and Anxiety Disorders Unitof the University of Turin, Departmentof Psychiatry of the Central Hospital of Bolzano, Psychiatric Hospital VillaSanta Chiara | 117 patients with DSM-IV MDD at Stage III according to Thase and Rush (1997) | Correlational study | A significant correlation was observed between baseline VascularEndothelial Growth Factorserum levels and the percentage reduction in depressive symptomatology after ECT (p = 0.003) |
| Bares et al., 2015 | Inpatients at Open Department of Prague Psychiatric Centre | 87 patients with DSM-IV MDD at least at Stage I according to Thase and Rush (1997) | Case-control study | The subjects were treated with various antidepressants. Areas under curve (AUC) of all three predictors (i.e., ≥ 20% reduction in MADRS total score at week 1 and 2, and the decrease of cordance at week 1) were not statistically different |
| Brakemeier et al., 2015 | Affective Research Unit of theDepartment of Psychiatry and Psychotherapy, University ofFreiburg Medical School | 70 patients with DSM-IV chronic depression and treatment resistance according to Thase and Rush (1997) | Case-control study | 75.7% of theintention-to-treat sample responded to Cognitive Behavioral Analysis System ofPsychotherapy, and 40% remitted. After 6 months75% and after 12 months 48% of patients sustained response |
| Kayser et al., 2015 | Department of Psychiatry and Psychotherapy atthe University Hospital of Bonn | 26 patients with DSM-IV current MDE at Stage II according to the Thase and Rush (1997) | Randomized clinical trial | A significant response to Magnetic Seizure Therapy was demonstrated by 69% of the patient sample, with 46% meeting remissioncriteria |
| Milanesi et al., 2015 | Villa S. Chiara PsychiatricHospital | 380 patients with DSM-IV MDD at Stage III according to Thase and Rush (1997) | Association study | An association between rs11218030 G allele and treatment-resistant depression was found |
| Desmyter et al., 2016 | part of a larger project | 50 patients with DSM-IV MDD and at least at Stage I according to Thase and Rush (1997)  | Randomized clinical trial | No differences were found between intermittent Theta Burst Stimulation and sham condition |
| Jha et al., 2016 | outpatient setting in a tertiary care general hospital in Northern India | 20 patients with DSM-IV-TR MDD at Stage II or III according to Thase and Rush (1997) | Randomized clinical trial | Patients who received high frequency rTMS over an area of hypoperfusion in the prefrontal cortex showed a significantly decrease of depressive symptoms compared to those who were administered rTMS in the left dorsoslateral prefrontal cortex area |
| Sugawara et al., 2016 | Department of Psy­chiatry of the Tokyo Women’s Medical University Hospital, Department of Psychiatry of the Tokyo Women’s Medical University Medical Center East, Fuku Clinic, Murakami Hospital, and Ms Clinic | 85 patients with DSM-IV MDE and at Stage I according to Thase and Rush (1997) | Retrospective cohort study | Aripiprazole augmentation remission rate was 36.5% |
| Yamamura et al., 2016 | Outpatients at Hiroshima University and regional hospitals | 16 patients with DSM-IV-TR MDD and current MDE at Stage 2 according to the Thase and Rush (1997) | Cross-sectional study | Patients with treatment resistance had increased right-thalamic fractionalamplitude of low-frequency fluctuations values compared with patients without treatment resistance |
| Benadhira et al., 2017 | trial | 58 patients with DSM-IV-TR unipolar depression and at least at Stage II according to Thase and Rush (1997) | Randomized clinical trial | A significant improvement in depressive symptoms was found only between the first month and the fourth month in active group in comparison with sham group |
| Fitzgerald et al., 2018 | referrals from both public hospital and private psychiatrists | 37 patients with DSM-IV MDE at Stage II according to Thase and Rush (1997) | Randomized clinical trial | No difference in the antidepressant effectiveness between the treatments (i.e., ECT or magnetic seizure therapy) was seen across any of the clinical outcome measures |
| Roulot et al., 2018 | Villa Santa Chiara Psychiatric Hospital | 45 patients with DSM-IV unipolar depression at Stage III according to Thase and Rush (1997) | Case-control study | No difference in the Sortilin-derived propeptide levels were found between patients and controls (p=0.92) |
| Çelik et al., 2019 | Inpatients at Department of Psychiatry, Gulhane Military School | 29 patients with DSM-IV MDD with treatment resistance defined according to Thase and Rush (1997) | Case-control study | ECT affects serum myostatin levels to a significant degree (p < 0.05) |
| Godin et al., 2019 | FondaMental Advanced Centers of Expertise in Resistant Depression cohort | 205 patients with DSM-IV MDE at least at Stage II according to Thase and Rush (1997) | Prospective non-comparative study | 38% of individuals with treatment-resistant depression met criteria for metabolic syndrome |
| Liao et al., 2019 | 8 psychiatric sites across China | 27 patients with DSM-IV MDD and at least at Stage II according to Thase and Rush (1997) | Prospective comparative study | Three categories were detected: severe depression (66%), moderate depression with anxiety (9%), mild depression with anxiety/somatization (25%). Remission rates were significantly different among anxious cases with severe (43.75%), moderate (22.73%), mild (26.25%) depression subtypes  |
| Maffioletti et al., 2019 | Psychiatric Hospital Villa Santa Chiara | 74 patients with DSM-IV MDD at Stage III according to Thase and Rush (1997) | Single-arm study | No difference in BDNF concentrations was observed in responders to ECT versus nonresponders, in remitters versus nonremitters, in sustained responders versus sustained nonresponders, and in sustained remitters versus sustained nonremitters  |
| Minelli et al., 2019 | Psychiatric Hospital Villa Santa Chiara | 27 patients with DSM-IV MDD at Stage III according to Thase and Rush (1997) | Single-blind randomized clinical trial | Lower depressive symptoms were observed among those who received Eye-Movement Desensitization and Reprocessing than among those who received trauma-focused Cognitive Behavioral Therapy (p = 0.04) |
| Yrondi et al., 2019 | University Hospital of Toulouse | 15 patients with DSM-5 MDD at least at Stage II according to Thase and Rush (1997) | Case-control study | At baseline, controls had significantly higher cortical thickness than patients in the fusiform gyrus, the inferior, middle and superior temporal gyrus, the parahippocampal gyrus and the transverse temporal gyrus. The difference was no longer significant after ECT |
| Correia-Melo et al., 2020 | local and nearby outpatient services | 63 patients with DSM-IV MDD with treatment resistant according to Thase and Rush (1997) | Randomized clinical trial | At 24 h, 24.1% in the ketamine group and 29.4% of participants in the esketamine group showed remission (p > 0.05) |
| Fitzgerald et al., 2020 | by referral from public and private psychiatrists | 74 patients with DSM-IV MDD at Stage II according to Thase and Rush (1997) | Randomized clinical trial | There were no significant differences in the degree of reduction in depressive symptoms, the rate of reduction in depressive symptoms, remission or response rates between the intensive Theta Burst Stimulation and the standard rTMS groups  |
| McIntyre et al., 2020 | Post-hoc chart review analysis | 297 patients with DSM-5 MDD or bipolar disorder treatment-resistant depression according to Thase and Rush (1997) | Retrospective cohort study | A meaningful change in depressive symptoms was found among treatment-resistant subjects receiving intravenous ketamine |
| Pardo et al., 2020 | physicians’ outpatient facilities | 25 patients with DSM-IV unipolar depressive disorder at Stage III according to Thase and Rush (1997) | Correlation study | Responders showed decreased metabolism with treatment in the right amygdala that correlated with clinical response |
| Barbini et al., 2021 | Mood disorders Unit at San Raffaele Turro,  | 56 patients with DSM-5 unipolar depression at Stage III according to Thase and Rush (1997) | Randomized clinical trial | All patients achieved the Stage II of Thase and Rush (1997).No differences were found between the two groups (rTMS vs rTMS plus bright light therapy) in terms of response rate and remission rate |
| Filipčić et al., 2021 | by referrals from daily hospitals or as outpatients | 40 patients with DSM-5 MDD at Stage II-IV according to Thase and Rush (1997)  | Single-arm study | Remission after rTMS with h1-coil was achieved by 38% and 42% after 10- and 15-day protocols, respectively |
| Herzog et al., 2021 | Affective Research Unit of the Department of Psychiatry and Psychotherapy, University of Freiburg Medical School | 70 patients with DSM-IV chronic depression and resistance to treatment according to Thase and Rush (1997)  | Prospective non-comparative study | 92.3% reported having experienced at least one negative effect, 45.2% indicated dependence on their therapist, experiences of stigmatization, 35.9% reported financial concerns, 33% had intrapersonal changes in terms of symptom deterioration |
| Hopman et al., 2021 | public outpatient clinics | 70 patients with DSM-IV MDD | Prospective non-comparative study | The level of treatment resistance was measured according to Thase and Rush (1997)Left dorsolateral prefrontal cortex - subgenual cingulate connectivity was not associated with treatment outcome |
| Rodrigues et al., 2021 | Canadian Rapid Treatment Center of Excellence | 332 patients with DSM-5 mood disorder and treatment-resistant depression according to Thase and Rush (1997) | Single-arm study | All sleep items, except for hypersomnia, were associated with an increased likelihood of achieving response or remission |
| Yrondi et al., 2021 | FACE-DR cohort of the French network, consisting of 13 specialty care centres located in academic psychiatric hospitals in France | 256 patients with a DSM-IV MDD at Stage II according to Thase and Rush (1997) | Cross-sectional study | In relation to suicide risk for the current depressive episode, an association was found with childhood trauma and it was mediated by the intensity of the current episode (total effect: β = 0.171; p = 0.011, direct effect: β = 0.135; p = 0.043; indirect effect: β = 0.036; p = 0.048) |
| **SOUERY ET AL. (1999)** |
| **Authors and date** | **Setting** | **Population** | **Design** | **Main results** |
| Manning et al., 2005 | ambulatory primary care sites in the University’s Department of Family Medicine’s residency training system or from the private psychiatricpractice of the Department of Family Medicine’s clinical faculty members | 23 patients with DSM-IV MDE, cyclothymic temperament, and treatment resistance according to Souery et al. (1999) | Naturalistic, open-label study | 70% had significant, sustained responses to lamotrigine. Of them, 75% were responders, 52% had remissions sustained longer than 12 months |
| Lin et al., 2020a | Psychosomatic Ward and Outpatient Department of the Kai-Syuan Psychiatric Hospital | 225 DSM-IV-TR MDD with an indication for ECT (i.e., need for a rapid and definitive response, high suicide risk, severe motor retardation, or treatment resistance depression according to Souery et al., (1999)) | Open-label trial | ECT-treated patients had significantly shorter time to resolution of suicidal ideation than fluoxetine-treated patients during acute treatment |
| Lin et al., 2020b | Inpatients enrolled at the Psychosomatic Ward of Kai-Syuan Psychiatric Hospital | 82 patients with DSM-5 MDD and treatment resistance according to Souery et al., (1999) | Randomized clinical trial | The two treatment groups (i.e., ECT plus agomelatine or ECT plus placebo) were comparable at score changes in symptom measures, functional impairment, quality of life, and neuropsychological tests  |
| Dalby et al., 2021 | Data collected in patients | 22 patients with DSM-IV MDD and ICD-10 moderate to severe depression | Cross-sectional study | None of the patients were chronic treatment resistant according to Souery et al. (1999).Patients revealed signs of capillary dysfunction in the anterior prefrontal cortex and ventral anterior cingulate cortex bilaterally and in the left insulate cortex compared to controls |
| **COREY-LISLE ET AL. (2002)** |
| **Authors and date** | **Setting** | **Population** | **Design** | **Main results** |
| Greenberg et al., 2004 | Employees with a medical or disability claim for ICD-9 MDD from a national Fortune 100 manufacturing company | 1,692 subjects | Retrospective cohort study | TRD was examined according to Corey-Lisle et al., (2002).The average annual cost of employees considered treatment resistant patients was $US14 490 per employee, while the cost for depressed but not treatment resistant employees was $US6665 per employee, and $US4043 for the employee from the randomsample |
| Ivanova et al. 2010 | Employees from 23 large US-based companies with claim for services  | 2,312 employees with at least one inpatient stay or at least two outpatient visits for ICD-9 diagnosis of MDD and with TRD examined according to Corey-Lisle et al., (2002) | Retrospective cohort study | TRD-likely employees had significantly higher rates of mental-health disorders, chronic pain, fibromyalgia, and comorbidity. Average direct 2-year costs were significantly higher for TRD-likely employees ($22,784) compared with major depressive disorder controls ($11,733) (p<0.0001) |
| Lepine et al., 2012 | medical records of patients seen at the Psychiatric Institute of the Clinics Hospital, School of Medicine, University of Sao Paulo | 212 patients with ICD-10 MDD | Retrospective cohort study | TRD was defined using the algorithm proposed by Corey-Lisle et al. (2002).TRD patients used significantly more resources from the psychiatric service compared to non-TRD patients |
| Scherrer et al., 2012 | Patient cohort | 536,415 patients with ICD-9 diagnosis of depression | Retrospective cohort study | An adaptation of Corey-Lisle et al. (2002) was used to assess TRD.Compared with treated patients, insufficiently treated patients were 3.04 (95% CI 2.12-4.35) times more likely and patients with treatment-resistant depression were 1.71 (95% CI 1.05-2.79) times more likely to die |
| Scherrer et al., 2016 | administrative extracts of electronic medical record | 6,169 patients with ICD-9 depression | Retrospective cohort study | An adaptation of Corey-Lisle et al. (2002) was used to assess treatment depression.Opioid use for 31–90 days and for >90 days, compared to 1–30 days, was significantly associated with new onset TRD (HR=1.25; 95%CI: 1.09‐1.45 and HR=1.52; 95%CI: 1.32‐1.74, respectively) |
| **FAVA (2003)** |
| **Authors and date** | **Setting** | **Population** | **Design** | **Main results** |
| Eschweiler et al., 2007 | Inpatients at three German study centres (Tuebingen, Freiburg, Ludwigsburg) and one Austrian centre(Rankweil) | 84 patients with ICD-10 MDE and treatment resistance according to Fava (2003) | Randomized clinical trial | 12 responders were found in each patient group (i.e., right unilateral ECT treatments or bifrontal ECT) |
| Chandler et al., 2010 | Outpatients enrolled by the local sites | 186 patients with DSM-IV MDD | Randomized clinical trial | The Massachusetts General Hospital Antidepressant Treatment Response Questionnaire is used to determine TRD.In 76.3% of the subjects, the number of failed adequate antidepressanttrials reported by the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire was concordant with the datacollected by medical monitors |
| Gibson et al., 2010 | MarketScan Commercial Claims and Encounters Database | 78,477 patients with ICD-9 depression | Retrospective cohort study | Two claims-based versionsof the Massachusetts General Hospital Treatment Resistant Depression staging method (Fava, 2003) (i.e., MGH; MGH-AD).The percentage of patients with scores > 3 (the cut-off for Treatment Resistant Depression) decreased by less than 1%-point from 28.8% (MGH) to 28.1% (MGH-AD) |
| Fava et al., 2012 | Multicenter study | 221 patients with DSM MDE and inadequate response to antidepressants as assessed via the Massachusetts General Hospital Antidepressant TreatmentResponse Questionnaire | Randomized clinical trial | The pooled, weighted response difference between aripiprazole 2 mg/day and placebo in the two phases was 5.6% (p = 0.18) |
| Pfeiffer et al., 2013 | Veterans Health Administration’sNational Registry ofDepression | 499 patients with an index ICD-9 depressivedisorder and a history of suicide cases | Case-control study | Treatment resistance wasmeasured according to Fava (2003). 11.6% of suicide cases had stage 3 or greater compared to 6.4% of controls (p < .001) |
| Fornaro et al., 2014 | Outpatients at the San Martino hospital of Genoa | 46 patients with DSM-IV current MDE with atypical features and a documented treatment resistance history according to Fava (2003) | Randomized clinical trial | By week 6, 21.7% of patients receiving duloxetine + placebo vs 26.1% of those receiving bupropion + placebo achieved response |
| Targum et al., 2014 | quality assurance program | 360 patients with DSM-IV-TR MDD and sufficient documentation of inadequate antidepressant responses as assed via the Massachusetts General Hospital Antidepressant TreatmentResponse Questionnaire | Randomized clinical trial | High correlations between site-based and site-independent raters (r=0.940 for all ratings) and high sensitivity, specificity, predictive values, and kappa coefficients for treatment response and non-response outcomes using the site-based rater scores as the standard. The blinded raters achieved 89.4% overall accuracy and 0.786 kappa for matching the treatment response or non-response outcomes of the site-based raters |
| Ball et al., 2015 | Outpatients enrolled by 56 investigators across the United States, Mexico, Chile, Brazil, the Netherlands, Spain, Lithuania | 608 patients with DSM-IV-TR MDD and inadequate response to antidepressant treatment asassessed via the modified Massachusetts General Hospital AntidepressantTreatment Response Questionnaire | Open-label study | 54% completed the open-label adjunctive treatment with edivoxetine. Mean improvements on depressive symptoms were observed from baseline to week 54 |
| Johnston et al., 2015a | Advanced InterventionsService in Dundee | 20 subjects with a lifetime history of treatment resistant DSM-IV depression who did not necessarily meet criteria fordiagnosis of depressive episode | Cross-sectional study | The level of treatmentnon-response was scored using the Massachusetts General Hospital clinical staging method.85% accuracy of individual subject diagnostic prediction was reported |
| Johnston et al., 2015b | Advanced Interventions Service in Dundee | 40 patients with DSM-IV MDD and treatment resistance according to Fava (2003) | Cross-sectional study | The dorsal raphe nucleus/ periaqueductal grey region of the midbrain and hippocampus were found to be overactive in major depressive disorder during unsuccessful loss-avoidance |
| Mirzakhani et al., 2015 | Department of Psychiatry at the Leiden University Medical Center  | 84 patients with DSM-IV MDD | Case-control study | Treatment resistance was assessed according to Fava (2003).No difference was observed in the prevalence of CYP2D6 phenotypes between the ECT and the control patients |
| Oakes et al., 2015 | 93 sites in 52 countries: Argentina, Belgium, Croatia, France, Germany, Greece, Italy, Korea, Mexico, Romania, Russia, Slovakia, Spain, Turkey, the United States | 292 patients with DSM-IV-TR MDD and inadequate response to current antidepressant treatment asassessed via the modified Massachusetts General Hospital AntidepressantTreatment Response Questionnaire | Open-label phase followed by a Randomized clinical trial | Comparing adjunctive edivoxetine with adjunctive placebo, differences were not significant for time to re-emergence of symptoms, rates of symptom re-emergence, or rates of sustained remission |
| Preskorn et al., 2015 | Study conducted at 12 sites in the United States | 120 patients with DSM-IV current MDD and no response to antidepressant treatment based on the Massachusetts General Hospital AntidepressantTreatment Response Questionnaire | Randomized clinical trial | GLYX-13 reduced depressive symptoms  |
| Davis et al., 2016 | Outpatients enrolled in 12 centersin the United States | 32 patients with DSM-IV MDD and inadequate response to antidepressant treatment according to the Massachusetts General Hospital AntidepressantTreatment Response Questionnaire | Open-label study | Improvements from baseline were observed at Week 6 (p < .0001) of brexpiprazole |
| Fava et al., 2016a | 15 sites in the United States | 54 patients with DSM-IV-TR MDD and inadequate response to antidepressant treatment as documented by the Massachusetts General Hospital Antidepressant TreatmentResponse Questionnaire | Open-label study | At week 6, clinically relevant improvements were observed with adjunctive brexpiprazole in irritability, anger-hostility, and depressive symptoms |
| Fava et al., 2016b | 31 sites in the United States | 142 patients with a DSM-IV-TR MDD and inadequate response to antidepressant treatment based on the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire | Randomized clinical trial | Compared with the placebo group, there were significantly greater improvements in 2 mg/2 mg buprenorphine/samidorphan or 8 mg/8 mg buprenorphine/samidorphan groups across depression outcome measures  |
| McAllister-Williams et al., 2016 | three centres, recruiting patients from 7 UK National Health Service Mental Health Trusts and localized primary care centres in the same region | 165 patients with DSM-IV MDE and treatment resistant depression according to Fava (2003) | Randomized clinical trial | At 5 weeks, depressive symptoms did not significantly differ between groups (metyrapone group vs placebo group) |
| Rotroff et al., 2016 | Two randomized controlled studies | 75 patients with a DSM-IV-TR MDD and inadequate response to antidepressant treatment based on the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire | Case-control study | Both ketamine and esketamine altered metabolites related to tryptophan metabolism and/or the urea cycle |
| Singh et al., 2016 | 14 sites in theUnited States | 67 patients with DSM-IV-TR recurrent MDD and inadequate response to antidepressant treatment as assessed by the Massachusetts GeneralHospital Antidepressant Treatment Response Questionnaire | Randomized clinical trial | In the twice-weekly dosing groups, the mean change in depressive symptoms at day 15 was -18.4 (SD=12.0) for ketamine and -5.7 (SD=10.2) for placebo; in the thrice-weekly groups, it was -17.7 (SD=7.3) for ketamine and -3.1 (SD=5.7) for placebo |
| Bernert et al., 2017 | series of clinical trials  | 54 patients with DSM-IV MDD | Observational study | Treatment resistant depression was measured according to Fava (2003).Suicidal ideation was associated with less NREM Stage 4 sleep, and higher nocturnal wakefulness |
| Carpenter et al., 2017 | Outpatients enrolled in a multi-centre study sponsored by Cervel Neurotech  | 75 patients with a DSM-IV MDD and treatment resistance in the currentepisode based on the Massachusetts General Hospital Antidepressant TreatmentResponse Questionnaire | Randomized clinical trial | Significantly greater improvement over time for the active (i.e., rTMS) versus sham group after 20 sessions (F = 7.174; p = 0.008) and also at the one-month follow-up (F = 6.748; p = 0.010) |
| Cusin et al., 2017 | referral by treating psychiatrists | 12 patients with DSM-IV MDD, history of failure to respond to antidepressant treatments during the current episodeas measured by theMassachusetts General Hospital AntidepressantTreatment History Questionnaire | Open-label study | After six ketamine infusions, 41.7% completers responded and 16.7% remitted |
| Freeman et al., 2017 | Review of independent remote SAFER Interviews conductedin 9 consecutive clinical drug trials | 2,734 independent remote SAFER Interviews were performed | Cross-sectional study | Raters administered also the Massachusetts General Hospital AntidepressantTreatment History Questionnaire.15.33% of patients who had been deemed eligible at research sites were not eligible after the structured interviews. The most common reason was that patients did not meet the study requirements for level of treatment resistance |
| Mathew et al., 2017 | three academic medicalcenters | 85 patients with DSM-IV-TR MDD and inadequate response to antidepressant treatment as assessed via the Massachusetts General Hospital Antidepressant Treatment ResponseQuestionnaire | Randomized clinical trial | Treatment groups (riluzole vs placebo) did not differ in mean change in depressive symptom severity, response rate, or in any secondary efficacy outcomes |
| Rachid et al., 2017 | Naturalistic clinical treatment study | 22 patients with DSM-IV unipolar MDD or bipolar disorder who failed to respond to antidepressant treatments during the current depressive episode according to Massachusetts General Hospital Antidepressant Treatment ResponseQuestionnaire | Single-arm study | There was a significant change in depressive symptoms severity from baseline to the end of week 4; 50% were responders and 40.9% achieved remission  |
| Daly et al., 2018 | 14 study sites (13 in the United States, 1 in Belgium) | 67 patients with DSM-IV-TR MDD and treatment resistance as assessed via the Massachusetts General Hospital Antidepressant Treatment ResponseQuestionnaire | Randomized clinical trial | Change (least squares mean [SE] difference vs placebo) in depressive symptoms in all 3 esketamine groups was superior to placebo (esketamine 28 mg: -4.2 [2.09], p = .02; 56 mg: -6.3 [2.07], p = .001; 84 mg: -9.0 [2.13], p < .001) |
| Hobart et al., 2018 | 75 sites in the United States, Russia, Poland, France, Serbia, Germany, Canada | 503 patients with DSM-IV-TR MDD and a current MDE and inadequate response to antidepressant treatments as assessed via the Massachusetts General Hospital Antidepressant Treatment ResponseQuestionnaire | Randomized clinical trial | Adjunctive brexpiprazole showed a greater improvement in depressive symptoms than adjunctive placebo (least squares mean difference [95% CI] = -1.48 [-2.56, -0.39]; p = .0078), whereas adjunctive quetiapine XR did not separate from placebo (-0.30 [-1.63, 1.04]; p = .66) |
| Lepola et al., 2018 | 34 sites in the USA, Finland, Estonia, Poland, and Germany | 132 patients with DSM-IV-TR MDD and an inadequate response to antidepressant treatment as assessed via the MassachusettsGeneral Hospital Antidepressant Treatment Response Questionnaire | Open-label study | 77.3% experienced ≥1 treatment-emergent adverse effect after flexible-dose brexpiprazole adjunct to antidepressant treatment |
| Olfson et al., 2018 | Truven Health Analytics MarketScanMedicaid Database | 5,801 patients with ICD-9 depression plus ICD-9 MDD  | Retrospective cohort study | Treatment resistance was assessed adapting the Fava (2003) model.25.9% of pharmacologically treated adults met criteria for treatment resistant depression. Compared with patients without TRD, TRD patients were significantly more likely to receive inpatient care for any cause (p < 0.001), a mental health-related reason (p < 0.001), or depression (p < 0.001) during the first year following their index antidepressant prescription |
| Targum et al., 2018 | 35 clinical trial sites in the United States | 234 patients with DSM-IV-TR MDE and an inadequate response to antidepressant treatments as assessed via the MassachusettsGeneral Hospital Antidepressant Treatment Response Questionnaire | Randomized clinical trial | There were no overall statistically significant differences found between MSI-195 added to ongoing antidepressant compared to placebo |
| Domany et al., 2019 | Out-patients referredfrom the community or the hospital’s ambulatory service | 41 patients with DSM-IV MDD | Randomized clinical trial | Treatment resistance was assessed according to Fava (2003).27.3% in the ketamine group achieved remissioncompared with none of the controls (p < 0.05) |
| Dubin et al., 2019 | Phase II study | 30 patients with DSM-IV-TR MDE and treatment-resistance as assessed via the Massachusetts General Hospital Antidepressant TreatmentResponse Questionnaire | Randomized clinical trial | Following the 3rd session, the effect of low field magnetic stimulation was superior to sham (F (1, 24) = 7.45, p = 0.03, Bonferroni-Holm corrected; F (1, 22) = 6.92, p = 0.03, Bonferroni-Holm corrected) |
| Fava et al., 2019 | Multicentre study | 207 patients with DSM-5 MDE and a current MDE and inadequate response to antidepressant treatments as assessed via the Massachusetts General Hospital Antidepressant TreatmentResponse Questionnaire | Randomized clinical trial | At week 5 of Stage 1, LS mean (SE) difference for pimavanserin versus placebo was significant for changes on depressive symptoms (p < .005) |
| Fedgchin et al., 2019 | Multi-center study in outpatient centers | 346 patients with DSM-5 recurrent or single episode MDD | Randomized clinical trial | Response to antidepressants in the current depressive episode were documented on the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire.Statistical significance was not achieved with esketamine 84 mg/antidepressant compared with antidepressant/placebo (least squares means difference [95% CI]: -3.2 [-6.88, 0.45]; 2-sided p value = .088) |
| Ionescu et al., 2019 | Outpatients recruited through referrals | 26 patients with DSM-IV MDD and history of failure of antidepressant treatment trials as assessed via the Massachusetts General Hospital Antidepressant TreatmentResponse Questionnaire | Randomized clinical trial | At three-month follow-up, two patients in each group (i.e., ketamine vs placebo) met criteria for remission from depression |
| Lex et al., 2019 | Michigan Biomarkers for Refractory Depression (Bluebird) study | 79 participants with DSM-IV/DSM-5 major depressive disorder or bipolar disorder. Medication resistance during the current episode was characterized using the Massachusetts General Hospital staging method | Prospective longitudinal | Patient-rated depressive symptoms correlated with physical (Pearson correlation, r = −0.26) and psychological (r = −0.43) QoL, whereas adverse childhood experiences correlated with environmental QoL (r = −0.33) |
| Newcomer et al., 2019 | across North America and Europe | 1,851 patients with DSM-IV-TR MDD and inadequate response to antidepressant treatments as assessed via the Massachusetts General Hospital Antidepressant TreatmentResponse Questionnaire | Randomized clinical trial | Mean body weight increase at last visit in the short-term studies was 1.5 kg with antidepressant + brexpiprazole and 0.3 kg with antidepressant + placebo. During long-term treatment, mean body weight increased by 3.8 kg over 58 weeks |
| Popova et al., 2019 | Multicenter study in Czech Republic, Germany, Poland, Spain, United States | 197 patients with DSM-5 MDD and documented nonresponse to antidepressant treatmentsbased on the Massachusetts General Hospital Antidepressant TreatmentResponse Questionnaire in the current depressive episode  | Randomized clinical trial | Change in depressive symptoms with esketamine plus antidepressant was significantly greater than with antidepressant plus placebo at day 28 (difference of least square means=-4.0, SE=1.69, 95% CI=-7.31, -0.64) |
| Clark et al., 2020 | part of a larger clinical trial | 16 patients with DSM-IV/DSM-5 MDD and chronic treatment resistant depression according to Fava (2003) | Single-arm study | Lower baseline glutamate predicted significant reduction in depressive symptoms (p = 0.018) and both depressive symptom reduction (p = 0.002) and 6-month response outcome (p = 0.013) |
| Jha et al., 2020 | EMBARCstudy atfour-sites | 293 patients with DSM-IV MDD who did not fail antidepressant trials as assessed via the Massachusetts General Hospital Antidepressant TreatmentResponse Questionnaire | Randomized clinical trial | With acute-phase treatment, participants with anger attacks experienced a greater reduction in irritability (p < 0.001) but not in depression (p = 0.813) or anxiety (p = 0.771) as compared to those without anger attacks |
| Kamiya et al., 2020 | 25 investigational sites in the US | 51 patients with current DSM-5 MDD | Randomized clinical trial | Response to the currentantidepressant treatment was confirmed usingthe Massachusetts General Hospital Antidepressant Treatment ResponseQuestionnaire.TS-121 groups showed greater numerical reductions compared to placebo  |
| Papakostas et al., 2020 | 12 US, non-academic sites | 220 patients with DSM-5 recurrent MDD without non-response to at least three antidepressanttrials as defined by the Massachusetts General Hospital Antidepressant TreatmentResponse Questionnaire | Randomized clinical trial | Depressive symptom reduction under NSI-189 versus placebo did not reach significance for dose |
| Wigmore et al., 2020 | family and population-based cohort of individuals within Scotland | patients with DSM-IV MDD, 250 had TRD and 3,202 had not | Retrospective cohort study | Treatment resistance was assessed following Fava (2003).No significant loci, genes or gene sets associated with antidepressant treatment resistance or stages of resistance were identified |
| Feeney et al., 2021 | part of a collaborative effort between the Massachusetts General Hospital Clinical Trials Network and Institute, multiple academic sites, and the National Institute of Mental Health. Outpatients were enrolled | 79 patients with DSM-IV-TR primary MDD and treatment resistance as assessed via the Massachusetts General Hospital Antidepressant TreatmentResponse Questionnaire | Randomized clinical trial | Among patients with a suicide score of ≥2 at baseline and <2 at day 3, the two groups (i.e., IV ketamine or IV midazolam placebo) did not differ significantly on mean scores changes at days 3, 5, 7, 14 or 30 |
| Heerlein et al., 2021 | Belgium, Germany, Italy, the Netherlands, Portugal, Spain, United Kingdom | 411 patients with DSM-5 or ICD-10 MDD or depressive disorder and treatment resistance as assessed via the Massachusetts General Hospital Antidepressant TreatmentResponse Questionnaire | Prospective non-comparative cohort study | After 6 months, only 16.7% achieved remission and 73.5% showed no response to a new treatment for depression according to routine clinical practice. At month 12, while 19.2% achieved remission and 69.2% showed no response, 33.3% of those in remission at month 6 were no longer in remission |
| Perugi et al., 2021 | Italian component of aEuropean, prospective, multicentric, observational cohort study | 124 in- and outpatients with DSM-5 or ICD-10 major depressive disorder or depressive disorder with treatment resistance as evaluated via the Massachusetts General Hospital-AntidepressantTreatment Response Questionnaire | Prospective comparative cohort trial | After 6months of treatment, clinical assessments were collected for 89 patients: 64 (71.9%)showed no response, 9 (10.1%) response without remission and 16 (18.0%) were in remission; non-responder patients showed lower quality of life and higher disability scores than responder patients |
| Shah et al., 2021 | claims data from a large US health plan for a commercially insured population | 21,180 adults with non-cancer pain and ICD-9/ICD-10 MDD | Retrospective cohort study | A claims-based algorithm developed from the Massachusetts General Hospital clinical staging method was used to assess treatment resistant depression.10.1% subjects were identified as treatment resistant. They had significantly higher average total costs and depression related costscompared with non-treatment resistant patients (all p < 0.001) |
| **FEKADU ET AL. (2009A) OR ITS ADAPTATIONS** |
| **Authors and date** | **Setting** | **Population** | **Design** | **Main results** |
| Fekadu et al., 2009b | tertiary research centre in the United Kingdom | 62 patients with DSM-IV depression and confirmed treatment resistant depression according to the Maudsley Staging Method | Prospective non-comparative cohort study | Higher odds of prediction for higher Maudsley Staging Method score were found for the occurrence of persistence depressive episode throughout follow-up (OR=2.01, 95%CI 1.14-3.54) and for the occurrence of depressive episodes lasting for 50% or longer of the follow-up period (OR = 2.11, 95% CI 1.25-3.57).An increase in Maudsley Staging Method score predicted spending about 1 extra week in a depressive episode, functional impairment, symptoms severity, persistence of depressive disorder.Among alternative Maudsley Staging Methods and individual staging components, only longer duration of the index depressive episode predicted being in a depressive episode for 50% or longer of the follow-up duration (OR=1.22, 95%CI 1.02-1.46). The Thase and Rush model also failed in predicting the outcome  |
| Fekadu et al., 2012  | Patients discharged from a tertiary unit for treatment-resistant mood disorders in the UK | 118 patients with ICD-10 TRD  | Prospective non-comparative cohort study | Participants with higher levels of treatment resistance defined using the Maudsley StagingMethod were less likely to achieve remission (hazard ratio (HR) = 0.77, 95% CI 0.68–0.99; p = 0.04) |
| Peeters et al., 2016 | University-affiliated outpatient treatment center or the daytime/inpatient unit for treatment –resistant depression of the Academic Medical Center | 274 patients with DSM-IV MDE | Data were collected both retrospectively and cross-sectionally | The Dutch Measure for quantification of Treatment Resistance in Depression (derived from the Maudsley Staging Method) was proposed:Episode duration: Acute (1), Sub-acute (2), Chronic (3) Symptom severity: Subsyndromal (1), Mild (2), Moderate (3), Severe without psychosis (4), Severe with psychosis (5)Functional impairment: No impairment (0), Mild impairment (1), Moderate impairment (2), Severe impairment (3)Comorbid anxiety symptoms: Notpresent (0), Present but not fulfilling DSM-IV criteria (0.5), Fulfilling at least 1 DSM-IV anxiety disorder (1)Comorbid personality disorder: Notpresent (0), Present not based on formal interview (0.5), Present based on formal interview (1)Psychosocial stressors: No (0), at least 1 (1)Treatment failures: Antidepressants Level 0: not used (0)Level 1: 1–2 medications (1)Level 2: 3–4 medications (2)Level 3: 5–6 medications (3)Level 4: 7–10medications (4)Level 5: >10medications (5)Augmentation/combinationLevel 0: not used (0)Level 1: 1–2 medications (1)Level 2: 3–4 medications (2)Level 3: 5–6 medications (3)Electroconvulsive therapy: Not used (0), Used (1)Psychotherapy: Not used (0), Supportive therapy (0.5), 1 empirically supported psychotherapy (1), at least 2 empirically supported psychotherapies (2) Intensified treatment: Not used (0), Daypatient treatment (1), Inpatient treatment (2)The tool showed excellent inter-/intra-rater reliability. Higher scores were associated with more symptoms and less remission during follow-up. The tool outperformed the Maudsley Staging Method in prediction of future depressive symptomatology. Remission was predicted equally well by both measures |
| Nakagawa et al., 2017 | University teaching hospital and a psychiatric hospital in Tokyo | 78 patients with DSM-IV MDD and treatment resistance according to Fekadu et al., (2009a) | Randomized clinical trial | Supplementing usual medication management with cognitive-behavioral therapy significantly alleviated depressive symptoms at 16 weeks and the treatment effect was maintained for at least 12 months (-15.4 vs -11.0; difference = -4.4; 95% CI, -7.2 to -1.6; p = .002) |
| Cladder-Micus et al., 2018 | local mental health institute (Pro Persona) and a university medicalcenter (Radboud University Medical Center, Centre for Mindfulness), referred by mental health care professionalsor recruited via flyers, posters, and websites | 106 patients with DSM-IV current MDE | Randomized clinical trial | Treatment resistance was assessed via the Peeters et al.’s (2016).Participants in the mindfulness-based cognitive therapy plus treatment as usual condition did not have significantly fewer depressive symptoms than those in the treatment as usual condition (–3.23 [–6.99 to 0.54], d=0.35, p=0.09) at post-treatment |
| Gobbi et al., 2018 | Mood Disorders clinic registry of McGill University Health Centre | 86 patients with DSM-5 MDD and treatment resistance according to Fekadu et al. (2009a) | Naturalistic study | Compared to T0, both treatments (i.e., antidepressant combinations or second-generation antipsychotics plus antidepressant augmentation) significantly decreased depressive symptoms (p<0.001) |
| Nuñez et al., 2018 | Medical charts of outpatients | 194 patients with DSM-IV MDE | Comparative study | The Maudsley StagingMethod (Fekadu et al., 2009a) was used to establish the severity of TRD.Comorbidity with anxiety disorders, higher depression scale scores and lower global assessment of functioning scores, and lower number of hospitalizations andpsychotherapies differentiated TR unipolar depression patients from bipolar disorder patients |
| Pisoni et al., 2018 | National Affective Disorders Unit, South London and Maudsley NHS Foundation Trust | 36 patients with a DSM-IV and ICD-10 affective disorder and with treatment-resistant, defined according to (Fekadu et al., 2009a) | Case-control study | Patients displayed lower serum levels of brain-derived neurotrophic factor(OR = 0.025; 95%CI = 0.001, 0.500) and vascular endothelial growth factor-C (OR = 0.083, 95% CI = 0.008, 0.839) and higher angiopoietin-1 receptor(OR = 2.651, 95% CI = 1.325, 5.303) compared to controls |
| van Belkum et al., 2018 | Netherlands Study of Depressionand Anxiety  | 829 subjects with DSM-IV MDD in the previous month or in the previous 6 months | Prospective comparative cohort trial | The Maudsley Staging Method was significantly associated with persistent depression (OR = 1.40, 95% CI 1.23-1.60, p < 0.001). Each point increase in the Maudsley Staging Method significantly predicted a worse course of depression over the following 2 years |
| van Diermen et al., 2018 | University Psychiatric Hospital of Duffel (part of the PROTECT cohort study) | 73 patients with DSM-IV-TR MDD or a severe depressive episode in bipolar disorder | Single-arm study | An adapted Maudsley Staging Method (Fekadu et al., 2009a) was proposed:Duration: acute (≤ 12 months) (score: 1), subacute (13-24 months) (score: 2), chronic (> 24 months) (score: 3).Symptom severity (at baseline): severe with psychosis (score: 1), severe without psychosis (score: 2), moderate (score: 3).Age: ≥ 65 years (score: 1), 50-65 years (score: 2), < 50 years (score: 3) The percentage of symptom reduction following ECT was best predicted by the Maudsley Staging Method (Fekadu et al., 2009) episode duration and depression severity factors (R2 completer sample 0.24) |
| van Dijk et al., 2019 | 7 locations of PsyQ, a nationwide organization providing outpatient secondary mental healthcare in the Netherlands. Anonymized data were extracted from the electronic patient records | 1,115 patients with DSM-IV-TR MDD or dysthymic disorder | Retrospective cohort srtudy | Higher Dutch Measure for Quantification of Treatment Resistance in Depression scores were associated with poorer outcomes during follow-up (i.e., longer-term prediction of symptom severity) |
| López-Solà et al., 2020 | Outpatients recruited from the adult Mental Health Unit of the Psychiatry Department at Parc Taulí Hospital | 229 patients with past or present DSM-IV TR MDD. Participants were subdivided into TRD and non-TRD according to (Fekadu et al., 2009a) | Comparative study | Low verbal memory scores (OR = 2.02; 95%CI 1.38–2.95) and high depressive symptom severity (OR = 1.29; 95%CI 1.01–1.65) were associated with TRD risk |
| Ma et al., 2020 | Inpatients at theGuangzhou Huiai Hospital | 37 patients with ICD-10 unipolar or bipolar depression | Observational study | The Maudsley StagingMethod (Fekadu et al., 2009a) was used to establish the severity of treatment resistance.The sample showed moderate treatment-resistance (Maudsley Staging Method = 7.30 ± 1.13) at admission. The treatment-resistant group had a smaller proportion of bipolar patients and more severe symptoms |
| van Eijndhoven et al., 2020 | outpatient clinic of the academic department ofpsychiatry of the Radboud UMC Nijmegen and mental health care institutePro-Persona Nijmegen in the Netherlands | 31 patients with DSM-IV MDD | Randomized clinical trial | Dutch method for quantification of treatment resistance in Depression (Peeters et al., 2016) was used to quantify the level of treatment resistance.There were no differences between the treatment arms (i.e., real and sham rTMS) |
| Evensen et al., 2021 | Psychiatric Centre Copenhagenand a psychiatrist’s clinic in the private sector in Copenhagen | 20 patients with DSM-IV MDE and treatment resistance according to (Fekadu et al., 2009a) | Single-arm feasibility trial | Compliance threshold of transcutaneous vagus nerve stimulation was reached for 80%; a statistically significant reduction in depression severity and an increase in cognitive speed were seen with unchanged suicidal ideation and sleep |
| Lucchese et al., 2021 | Medical records of the Psychiatry Department of the Federal University of Sao Paulo | 70 patients with DSM-IV MDD | Retrospective cohort study | The Maudsley Staging Method (Fekadu et al., 2009a) was used to assess the treatment resistance.At baseline, the sample presented with severe treatment resistance in 65.7% and 47.1% had anxiety disorder comorbidity. The response rate to esketamine was 50%. A better outcome was predicted by mild and moderate Maudsley Staging Method scores (OR = 3.162, p = 0.041) |
| Sado et al., 2021 | two outpatient clinics in Tokyo, namely a university hospital and a psychiatric hospital | 80 patients with DSM-IV MDD and at least a minimaldegree of treatment resistance according to Fekadu et al., (2009a) | Cost-effectiveness study | The incremental cost-effectiveness ratios were JPY -15 278 322 and 2 026 865 for pharmacotherapy-resistant depression for all samples and those with moderate/severe symptoms at baseline, respectively |
| **CONWAY ET AL. (2017)** |
| **Authors and date** | **Setting** | **Population** | **Design** | **Main results** |
| Bang Madsen et al., 2020 | From the Danish National Prescription Registry | 129,945 patients who redeemed their first antidepressive prescription between 2005 and 2012. Treatment rsistant depression was defined *a priori* based on Conway et al., (2017) | Prospective comparative cohort trial | During follow up, 17% of patients with treatment resistant vs 8% of non-treatment resistant depression patients received disability pension, resulting in greater risk of premature workforce exit (adjusted HR = 3.23; 95% confidence interval 3.05–3.43) |
| **MORE THAN ONE TREATMENT-RESISTANCE DEPRESSION STAGING MODEL** |
| **Authors and date** | **Setting** | **Population** | **Design** | **Main results** |
| Petersen et al., 2005 | charts of patients at Massachusetts General Hospital and Brown University | 115 patients treated withinthe last 3 years, with a DSM-IV MDD | Retrospective cohort study | For each one-point increase in the MassachusettsGeneral Hospital staging method staging scoreand one level increase in the Thase and Rush (1997) staging method staging score, there was a 271% and 91% increase in the chance for non-remission to treatment, respectively |
| Gervasoni et al., 2009 | Outpatients of the GODS observational study | 20 patients with DSM-IV severe MDE | Seven-step treatment study | According to Thase and Rush (1997) all patients met criteria for StageII. According to Fava (2003), all patients scored between 1.5 and 2 on theMassachusetts General Hospital scale |
| Piccinni et al., 2009 | Inpatients at Dipartimento di Psichiatria, Neurobiologia, Farmacologia eBiotecnologie, University of Pisa | 18 patients with DSM-IV-TR MDE and treatment resistant depression according to Thase and Rush (1997) and Fava (2003) | Case-control study | Only remitters who showed higher baseline BDNF levels reached normalized BDNFlevels after ECT |
| Christmas et al., 2011 | Subjects who underwent thermalanterior capsulotomy in Dundee from 1992 | 20 patients with ICD-10 MDD and treatment resistance according to the Massachusetts’ GeneralHospital Scoring Method, and classified using the Thase andRush (1997) | Prospective non-comparative study | At long term follow-up after thermalanterior capsulotomy, 50% were classified as ‘responders’ and 40% as ‘remitters’; 55% were classified as ‘improved’; 35% as ‘unchanged’; and 10% had ‘deteriorated’ |
| Hazari et al., 2013 | Data obtained from clinical case notes at primary care, Dundee affective disorders clinic, secondary or tertiary care referrals | 112 patients with ICD-10 Depressive Episode | Retrospective cohort study | In addition to scores on the Thase and Rush (1997) model, Massachusetts General Hospital staging method, the Antidepressant treatment history form, an additional score was calculated: the ‘Dundee antidepressant treatment adequacy’ (DATA) score with the aim to measure treatment resistance along with the adequacy of past treatments.The DATA score was calculated by the following formula: (Massachusetts General Hospital staging score + Thase and Rush Stage III) + composite score for all treatments) x Treatment Precision Index.There is a considerable degree of overlap between the confidence intervals of each of these groups |
| Ruland et al., 2016 | inpatients from three different centres | 65 patients with DSM-IV-TR MDD and treatment resistance according to Thase and Rush (1997), Fekadu et al., (2009a) | Cross-sectional study | Significant changes of three apolipoproteinsA–I (β = 0.029, p = 0.035), M (β = −0.017, p = 0.009) and F(β = −0.031, p = 0.024) were associated with the Thase and Rush (1997) model but notthe Fekadu et al., (2009a) model |
| Mello et al., 2021 | Secondary analysis from a randomized controlled trial | 61 patients with DSM-IV MDD and treatment resistance according to Thase and Rush (1997), Petersen et al., (2005), Fekadu et al., (2009a) | Randomized controlled trial | Subjects with high trait dissociation had a higher risk of induced dissociation state (relative risk [RR] 1.41, 95% CI 1.11-1.78) and very high induced dissociation (RR 3.05, 95% CI 1.14-8.15) by ketamine or esketamine  |

MDE: Major Depressive Episode; MDD: Major Depressive Disorder; rTMS: repetitive transcranic Magnetic Stimulation; ECT: Electroconvulsive Therapy; MDE: Major Depressive Episode; TRD: Treatment Resistant Depression; N/A: Not Applicable

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