Supplementary information

Representation and outcomes of individuals with major depression in routine care who are ineligible for randomized controlled trials: a nationwide register-based study

World Psychiatry 2026

Aleksi Hamina & Justo Pinzón-Espinosa, Heidi Taipale, Johannes Schneider-Thoma, Joaquim Radua, Orestis Efthimiou, Narcís Cardoner, Christoph U. Correll, Paolo Fusar-Poli, Ellenor Mittendorfer-Rutz, Brenda W.J.H. Penninx, Henricus G. Ruhe, Antti Tanskanen, Christiaan Vinkers, Stefan Leucht, Eduard Vieta, Andrea Cipriani, Jari Tiihonen, Jurjen J. Luykx

RCT exclusion criteria

The typical RCT exclusion criteria were derived from recently published meta-analyses on both the acute pharmacological treatment of MDD and the maintenance pharmacological treatment of MDD.[1,2]
Several consensus sessions were held with all contributors to harmonize these criteria across the meta-analyses and to generate a list that best represents exclusion criteria used in antidepressant trials.

List of Studies from which Inclusion and Exclusion Criteria were Derived

Boulenger 2012

Inclusion criteria: Patients in remission (MADRS total score ≤10) at both Weeks 10 and 12 were randomized to the double-blind, placebo-controlled, fixed-dose treatment period.... Patients with a primary diagnosis of MDD according to DSM IV-TR criteria (American Psychiatric Association, 2000) presenting with an MDE of at least four weeks' duration and at least one prior MDE were included in the trial if they were an in- or outpatient of either sex, aged from 18 to 75 years, with a MADRS total score ≥26 at both the screening and baseline visits.

Exclusion criteria: Patients were excluded if they had any current psychiatric disorder other than MDD as defined in the DSM-IV-TR (assessed using the Mini International Neuropsychiatric Interview (MINI)) (Lecrubier et al., 1997), or if they had a current or past history of manic or hypomanic episode, schizophrenia or any other psychotic disorder, including major depression with psychotic features, mental retardation, organic mental disorders, or mental disorders due to a general medical condition, any substance abuse disorder (except nicotine and caffeine) within the previous six months, presence or history of a clinically significant neurological disorder (for example, Alzheimer's disease, Parkinson's disease, multiple sclerosis and Huntington disease) or any Axis II disorder that might compromise the study. Patients at serious risk of suicide, based on the investigator's clinical judgment, or who had a score ≥5 on item 10 of the MADRS scale (suicidal thoughts) were also excluded, as were those receiving formal behaviour therapy or systematic psychotherapy, or were pregnant or breast-feeding, or whose current depressive symptoms were considered by the investigator to have been resistant to two adequate antidepressant treatments of at least six weeks' duration, or had previously been exposed to Lu AA21004. Patients had to be withdrawn if they became pregnant during the study, if the investigator considered it to be in the best interest of the patient for safety/efficacy reasons, if laboratory values were outside normal ranges and were considered by the investigator to be a potential safety risk, if they were considered to be at significant risk of suicide, if they scored ≥5 points on item 10 (suicidal thoughts) of the MADRS, if the randomization code for a patient was broken, if consent to participate was withdrawn, if they did not take study medication for more than six consecutive days, or if the patient was lost to follow-up. The patient could be withdrawn from the study if a serious adverse event (SAE) (death, life-threatening condition, hospitalization) occurred. If adverse events (AEs) were contributory to withdrawal, they were always regarded as the primary reason for withdrawal. Patients completing the open-label period had to be withdrawn if they did not fulfil the remission criterion at Week 10 or Week 12.

Dalery 2001

Inclusion criteria: To be selected for the first treatment phase, patients were required to be aged >=18 years and <= 70 years and to meet DSM-III-R criteria for a moderate or severe major depressive episode. A score 17 on the first 17 items of the 21-item Hamilton depression rating scale (HDRS) (Hamilton, 1960) was also required, together with at least one major depressive episode in the previous 5 years. … Informed patient consent was obtained on entry into this phase of the study. Informed patient consent was obtained on entry into this phase of the study. At this phase patients could be either hospitalized or ambulatory; they were seen at four visits on D1, D7, D21, and D42. 1. they were considered on D42 to be treatment responders, i.e. if their overall HDRS score had decreased by >=50% vs D1 and was <15; and 2. the investigator considered that the patients' response to treatment was satisfactory and enabled them to commence the double-blind treatment phase.

Exclusion criteria: Patients with a history of manic episodes were not included. Other noninclusion criteria were the following: a history of lithium therapy; antidepressant therapy in the preceding 2 weeks; electroconvulsant therapy in the preceding 6 months; absence of effective contraception (oral contraceptive or intrauterine device) in women of child-bearing age; pregnancy and breastfeeding; documented active hepatic, cardiovascular, neurological, metabolic, or malignant disease; and DSM-III-R criteria for drug or alcohol abuse or dependency.

Dobson 2008

Inclusion criteria: The participants for this study consisted of adult outpatients who responded to acute phase treatment for depression from the Dimidjian et al. (2006) study, based in Seattle, WA. Participants in that study met criteria for Diagnostic and Statistical Manual of Mental Disorders (4th ed.; American Psychiatric Association, 1994) major depressive disorder on the basis of diagnostic interviews, had scores of 20 or above on the Beck Depression Inventory II (BDI-II; Beck, Steer, & Brown, 1996) and scores of 14 or above on the 17-item version of the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960), and did not meet criteria for a number of common exclusion diagnoses in depression psychotherapy studies. The University of Washington institutional review board approved the protocol. 1 All participants provided written informed consent prior to enrollment in the study. *(no other inclusion criteria given in Dimidjian 2006)*

Exclusion criteria *(From Dimidjian 2006)***:** Participants were excluded if they had a lifetime diagnosis of psychosis or bipolar disorder, organic brain syndrome, or mental retardation. Additional exclusion criteria included the following: substantial and imminent suicide risk; a current (e.g., within the past 6 months) or primary diagnosis of alcohol or drug abuse or dependence or a positive toxicology screen; a primary diagnosis of panic disorder, obsessive–compulsive disorder, psychogenic pain disorder, anorexia, or bulimia; or presence of antisocial, borderline, or schizotypal personality disorder. In addition, participants who had not responded favorably within the preceding year to an adequate trial of either CT or paroxetine also were excluded. Because medications were administered in the trial, individuals also were required to have satisfactory results from a physical examination, laboratory screen (complete blood count, complete metabolic panel, thyroid screen including TSH, T3, T4, and urinalysis), and electrocardiogram (if over 40 years of age). Participants were excluded if they had an unstable medical condition, were using any medication that would complicate the administration of paroxetine or had a known allergy to paroxetine. Moreover, women were not enrolled if pregnant, lactating, or not using suitable contraception if capable of becoming pregnant.

Doogan 1992

Inclusion criteria: Patients who presented to either psychiatric out-patient clinics or family practitioners were screened for suitability, and all were required to give informed consent before entering the study. Patients between 18and 70 years of age who met DSM III criteria for major depressive disorder were considered eligible (although some older patients were included). Participation was limited to those with a minimum baseline score on the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960) of 17 on the first 17 items. Women participants were to employ adequate contraceptive measures, be post-menopausal or be sterile as a result of a surgical procedure. During the first eight weeks, sertraline was prescribed on an open-label basis. Thereafter, if the response was satisfactory and both patient and investigator agreed, either sertraline or placebo was given on a double-blind randomised basis for 44 weeks following the open-label run-in.

Exclusion criteria: Those excluded from the study comprised pregnant or lactating women; persons whose depression was secondary to other forms of psychiatric illness or organic disease, puerperium or drugs; concurrent psychotropic drugs except chloralhydrate or short-acting benzodiazepines for insomnia; and anyone with significant physical disease, drug or alcohol dependence; or a history of peptic ulceration. Hypersensitivity or resistance to antidepressant drugs and receipt of a monoamine oxidase inhibitor in the 14 days before beginning the drug trial were also grounds for exclusion.

Feiger 1999

Inclusion criteria: Outpatients of either sex who were 18 years of age or older with a DSM-III-R diagnosis of major depressive disorder (single episode with duration of at least one year, or a recurrent episode of at least 6 months duration), able to give informed consent, judged to be free of significant personality dysfunctioning, and having a baseline score of 20 or more on the HAMDS were enrolled. …For the purpose of randomization and entry into the double-blind trial, patients were defined to be in stable remission at the end of single-blind treatment if they had: (1) achieved a Hamilton Depression Scale (HAMDS) total score ≤ 10 on two consecutive visits at least 7 days apart from week 6 through week 10, with no two consecutive HAMDS scores > 10 thereafter, and (2) had a HAMDS score ≤ 10 at the week 16 visit and at the previous visit (occurring at least 7 days earlier). Thus, only patients who demonstrated a stable remission over at least the last 8 weeks of the 16-week single-blind treatment portion were eligible for entry into the double-blind continuation trial.

Exclusion criteria: Patients who were pregnant or lactating, had a concurrent DSM-III-R Axis I diagnosis of mood disorders other than nonpsychotic major depression, organic mental syndromes or disorders, or any psychotic disorder were not enrolled. Use of MAOIs or electroconvulsive therapy (ECT) within 4 weeks of the start of treatment was prohibited. All patients who had been at steady state with anxiolytic or antidepressant drugs other than fluoxetine prior to entry had a 2-week washout period. The washout period for fluoxetine was 4 weeks.

Gilaberte 2001

Inclusion criteria: Patients were male and female outpatients, 18 to 65 years of age, who met DSM-III-R criteria for unipolar major depression and had at least one previous major depressive episode in the last 5 years. Patients scored at least 18 on the 17-item Hamilton Rating Scale for Depression (HAM-D-17) and at least 4 on the Clinical Global Impression (CGI) Severity scale in the index episode. Patients who met criteria for remission of the depressive episode after 8 weeks of acute treatment (who no longer met the diagnostic criteria for major depression per DSM-III-R and had HAM-D-17 scores of <=8 and CGI Severity scores of <= 2) entered the continuation period of phase 2. Patients who met remission criteria by the eighth week (acute treatment) of phase 2 and maintained remission during the remaining 24 weeks (continuation treatment) of phase 2 were randomized to phase 3, which consisted of 48 weeks of double-blind maintenance treatment with either fluoxetine 20 mg/day or placebo.

Exclusion criteria: Only patients who had received no pharmacologic treatment during the current depressive episode were admitted. Patients with other axis I diagnoses, organic mental disorders, a history of drug abuse, or severe physical illness or who were at risk for suicide were excluded. Pregnant or breast-feeding women and women of childbearing potential not using adequate contraceptive measures were also excluded from the protocol. Patients resistant to pharmacologic treatment during previous depressive episodes were also excluded.

Goodwin 2013

Inclusion criteria: Patients eligible for this study were male or female outpatients with a primary diagnosis of MDD and a current major depressive episode assessed as moderate or severe, according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria. All patients included gave written informed consent to participate. The recurrent MDD episode was required to have started at least 8 weeks before selection. Patients were selected on the basis of a minimum of two episodes within the last 3 years or a minimum of three episodes within the last 5 years. The MDD episode could be with or without melancholic features according to DSM-IV-TR criteria, but without a seasonal pattern or psychotic features and without postpartum onset. Patients aged 18 to 65 years were eligible if they had an HDRS-17 total score ≥ 22, a sum of items 1 (depressed mood) + 2 (feelings of guilt) + 5 (insomnia: middle in the night) + 6 (insomnia: early hours of the morning) + 7 (work and activities) + 8 (retardation) + 10 (psychic anxiety) + 13 (general somatic symptoms) of HDRS-17 ≥ 55% of HDRS-17 total score, a Clinical Global Impression-Severity of Illness scale (CGI-S) score ≥ 4, and a Hospital Anxiety Depression Scale 19

depression sub score ≥ 11. The Sheehan Disability Scale, 20 a questionnaire that assesses 3 items (work, social life, and family life/home responsibilities) for how much the symptoms of depression have been disruptive, had to be filled in by patients at selection. Patients eligible to enter the randomization phase had to meet the following criteria: 17-item-Hamilton Depression Rating Scale (HDRS-17) 17 total score ≤ 10 and Clinical Global Impressions-Improvement scale (CGI-I) 18 score ≤ 2 at week 8 or week 10 at the latest.

Exclusion criteria: The patients were required to be physically healthy or to have stabilized significant illnesses on the basis of medical history, physical examination, 12-lead electrocardiogram, and clinical laboratory tests (biochemistry and hematology). Patients with any of the following disorders from DSM-IV-TR, identified with the Mini-International Neuropsychiatric Interview, 21 were excluded: (1) chronic depression (> 2 years of a depressive episode); bipolar disorder I and II; major depressive disorder superimposed on dysthymic disorder according to DSM-IV-TR (double depression); current panic disorder; obsessive-compulsive disorder; posttraumatic stress disorder; acute stress disorder; schizoaffective disorder of depressive type; or any other psychotic disorder, including major depression with psychotic features; or (2) alcohol or drug abuse or dependence within the past 12 months and any personality disorder that might compromise the study. Patients were also excluded if they were at risk for suicide according to the investigator or had a rating of 4 points on item 3 of HDRS-17. Patients were also excluded if they had received any of the following recent/concomitant therapies: insight-oriented and structured psychotherapy (interpersonal therapy, psychoanalysis, cognitive-behavioral therapy) started within 3 months of inclusion; light therapy started within 2 weeks; oral antipsychotic drugs within 4 weeks; depot neuroleptics within 6 months; electroconvulsive therapy (ECT) within the last 3 months, requiring ECT at the moment (according to investigator's clinical judgment); or lithium/ anticonvulsants within 4 weeks. Washout times required for other medications were usually 1 week for antidepressants (3 weeks for fluoxetine, 2 weeks for nonselective monoamine oxidase inhibitors). All benzodiazepines had to be stopped at the time of selection (at the latest). Only zolpidem could be taken until week 2 (1 tablet per night) in case of insomnia not tolerated by the patient. In addition, patients with a current depressive episode resistant to 2 different previous antidepressant treatments of at least 4 weeks' duration at appropriate dose and patients who had demonstrated a lack of response to previous treatment with agomelatine (including current episode) were excluded.

Goodwin 2009

Inclusion criteria: Patients eligible for this study were male or female outpatients with a primary diagnosis of MDD and a current major depressive episode assessed as moderate or severe, according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria. All patients included gave written informed consent to participate. The recurrent MDD episode was required to have started at least 8 weeks before selection, and patients were to have been previously free of significant symptoms for at least 6 months. The MDD episode could be with or without melancholic features according to DSM-IV-TR criteria, but without a seasonal pattern or psychotic features and without postpartum onset. Patients aged 18 to 65 years were eligible if they had an HDRS-17 total score ≥ 22, a sum of items 1 (depressed mood) + 2 (feelings of guilt) + 5 (insomnia: middle in the night) + 6 (insomnia: early hours of the morning) + 7 (work and activities) + 8 (retardation) + 10 (psychic anxiety) + 13 (general somatic symptoms) of HDRS-17 ≥ 55% of HDRS-17 total score, a Clinical Global Impression-Severity of Illness scale (CGI-S) score ≥ 4, and a Hospital Anxiety Depression Scale 19 depression sub score ≥ 11. The Sheehan Disability Scale, 20 a questionnaire that assesses 3 items (work, social life, and family life/home responsibilities) for how much the symptoms of depression have been disruptive, had to be filled in by patients at selection. Patients eligible to enter the randomization phase had to meet the following criteria: 17-item-Hamilton Depression Rating Scale (HDRS-17) 17 total score ≤ 10 and Clinical Global Impressions-Improvement scale (CGI-I) 18 score ≤ 2 at week 8 or week 10 at the latest.

Exclusion criteria: The patients were required to be physically healthy or to have stabilized significant illnesses on the basis of medical history, physical examination, 12-lead electrocardiogram, and clinical laboratory tests (biochemistry and hematology). Patients with any of the following disorders from DSM-IV-TR, identified with the Mini-International Neuropsychiatric Interview, 21 were excluded: (1) chronic depression (> 2 years of a depressive episode); bipolar disorder I and II; major depressive disorder superimposed on dysthymic disorder according to DSM-IV-TR (double depression); current panic disorder;

obsessive-compulsive disorder; posttraumatic stress disorder; acute stress disorder; schizoaffective disorder of depressive type; or any other psychotic disorder, including major depression with psychotic features; or (2) alcohol or drug abuse or dependence within the past 12 months and any personality disorder that might compromise the study. Patients were also excluded if they were at risk for suicide according to the investigator or had a rating of 4 points on item 3 of HDRS-17. Patients were also excluded if they had received any of the following recent/concomitant therapies: insight-oriented and structured psychotherapy (interpersonal therapy, psychoanalysis, cognitive-behavioral therapy) started within 3 months of inclusion; light therapy started within 2 weeks; oral antipsychotic drugs within 4 weeks; depot neuroleptics within 6 months; electroconvulsive therapy (ECT) within the last 3 months, requiring ECT at the moment (according to investigator's clinical judgment); or lithium/ anticonvulsants within 4 weeks. Washout times required for other medications were usually 1 week for antidepressants (3 weeks for fluoxetine, 2 weeks for nonselective monoamine oxidase inhibitors). All benzodiazepines had to be stopped at the time of selection (at the latest). Only zolpidem could be taken until week 2 (1 tablet per night) in case of insomnia not tolerated by the patient. In addition, patients with a current depressive episode resistant to 2 different previous antidepressant treatments of at least 4 weeks' duration at appropriate dose and patients who had demonstrated a lack of response to previous treatment with agomelatine (including current episode) were excluded.

Hochstrasser 2001

Inclusion criteria: Patients were in- and out-patients recruited from 54 centres (psychiatric institutions and, in the UK, general practitioner research settings) between November 1995 and January 1997 in nine European countries (Austria, Belgium, Finland, France, Italy, The Netherlands, Norway, Switzerland and the UK). They were of either gender, aged 18–65 years, suffering from unipolar, recurrent major depressive episode (DSM-IV, 296.3; American Psychiatric Association, 1994), had a total score ≥22 on the Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979) and had had two or more major depressive episodes prior to the index episode, the last one within the past 5 years.

Exclusion criteria: Patients were excluded from the study if: the index episode had lasted more than 6 months; they had a history of schizophrenia, (hypo)mania, epilepsy, drug or alcohol misuse; a family history of bipolar disorder; or they suffered from severe somatic disorders. Similarly, patients were excluded if they had been treated recently with other antidepressants or electro-convulsive therapy (3 days to 8 weeks before entry, depending on treatment type), if they had a score ≥ 5 for MADRS item 10 (suicidality) or if they were pregnant.

No concomitant psychotropic medication was allowed, except benzodiazepines and other hypnotics, the dose of which was to remain unchanged after week 8 of Period II and which could not be started in Periods II or III except in the case of relapse/recurrence.

All patients gave written informed consent prior to inclusion.

Keller 1998

Inclusion criteria: Outpatients meeting a structured clinical interview diagnosis of chronic major depression (of at least 2 years' duration), or dysthymic disorder with a concurrent diagnosis of major depression ("double depression") based on the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R) were enrolled. Patients who had a minimum baseline severity of 18 on the 24-item Hamilton Depression scale (HAM-D) after a 1-week single-blind placebo lead-in were initially entered into the 3-phase protocol. During the acute phase, patients were randomized in the double-blind study to 12 weeks of treatment with either sertraline hydrochloride or imipramine hydrochloride in a 2:1 ratio. Patients next entered a 4-month continuation phase if, at the end of the acute phase, they fell into either (1) the full remission response category, which is operationally defined as achieving a final HAM-D total score of 7 or less and a Clinical Global Impressions (CGI) improvement score of 1 or 2 (very much or much improved) or (2) the

satisfactory therapeutic response category, which is operationally defined as achieving a reduction of 50% in the final HAM-D total score, as well as a score of 15 or less, a CGI improvement score of 2 or less, and a CGI severity score of 3 or less. Of the patients who received the sertraline treatment, 209 (49.1%) of 426 both completed 12 weeks of acute treatment and met full or satisfactory response criteria. These 209 patients were eligible for entry into the continuation phase of treatment. Patients were eligible to enter the maintenance phase reported if they had sustained at least a satisfactory antidepressant response to sertraline through the end of continuation therapy.

Exclusion criteria: Not explicitly reported.

Kocsis 2007

Inclusion criteria: Clinical diagnosis for recurrent major depression

Exclusion criteria: The patient has failed on an adequate trial of fluoxetine, venlafaxine or venlafaxine ER during the current episode of major depression, or the patient is treatment-resistant; b) Known hypersensitivity to venlafaxine or fluoxetine; c) History or presence of clinically significant hepatic, cardiovascular or renal disease, or other serious medical disease, including history of seizure disorder

McGrath 2006

Inclusion criteria: Diagnoses were established using the Structured Clinical Interview for DSM-IV Axis I Disorders—Patient Edition (21). No minimum score for severity of depressive symptoms was required for inclusion in the study.

Exclusion criteria: Patients were excluded from the study if they were at significant risk of suicide; were pregnant or breast-feeding; were women not using effective contraception; had an unstable physical disorder; had a lifetime history of any organic mental disorder, psychotic disorder, or mania; had a history of seizures; had a neurological disorder that significantly affects CNS function; had been active substance abusers or had substance dependence in the previous 6 months, other than nicotine dependence; were taking medications that may cause or exacerbate depression; had clinical or laboratory evidence of hypothyroidism without adequate and stable replacement therapy; or had a history of nonresponse to an adequate trial of a selective serotonin reuptake inhibitor (defined as a 4-week trial of at least 40 mg of fluoxetine or the equivalent daily).

Montgomery 1993

Inclusion criteria:

All patients entering the study were required to fulfil conventional criteria for inclusion in acute efficacy studies in depression, namely DSM-III-R criteria for unipolar major depression of moderate or greater severity [score on the Hamilton Depression Scale (21 item) (HAMD) of 18 or more] with at least two weeks duration. All patients were required to satisfy recurrence rate criteria of three episodes – the recent episode plus two – in the four years before entering the study.

Exclusion criteria:

Patients with significant physical illness, pregnancy, dementia or drug abuse were excluded as were patients who had received ECT over the past three months or neuroleptics over the past four weeks. Patients with abnormal laboratory safety values were also excluded. Patients were aged between 18 and 65 years and were treated in five psychiatric out-patient centres. All gave written informed consent.

Montgomery 2004

Inclusion criteria:

Outpatients 18 years or older who met DSM-III-R criteria for major depression were eligible to participate in the study if they had a history of recurrent major depression (≥ 1 previous episode in the last 5 years with a symptom-free period of > 6 months between episodes) and symptoms of depression for > 1 month before study entry. Eligible subjects had to have a 21-item Hamilton Rating Scale for Depression ($HAM\text{-}D_{21}$) score of ≥ 20 at the pre-study screening and at the baseline visit, and no more than a 20% decrease in $HAM\text{-}D_{21}$ scores between the 2 evaluations.

Exclusion criteria: Patients with a history of drug or alcohol dependence as defined by DSM-III-R criteria within 2 years of the start of the open treatment period were excluded. Subjects with a recent history of myocardial infarction; history of hepatic or renal disease; seizure disorder, psychotic disorder, or bipolar disorder; or hypersensitivity to venlafaxine were excluded from participation, as were pregnant or breastfeeding women and patients with concomitant psychiatric disorders meeting DSM-III-R criteria.

Montgomery 1993a

Inclusion criteria: Eligible patients were between the ages of 18 and 70 years met DSM-III-R criteria for major depression, and had a score of 22 or more on the Montgomery-Asberg Depression Rating Scale (MADRS, Montgomery and Asberg, 1979) at the start of the acute, placebo-controlled study.

Exclusion criteria: Exclusion criteria included pregnancy, lactation, and duration of depression of more than 12 months. Those patients who responded (MADRS score ≤ 12) to 20 or 40 mg citalopram, or to placebo at six weeks were eligible for entry into the present 24-week study.

Perahia 2006

Inclusion criteria: All of the study participants (both men and women) were at least 18 years of age. Ethics review boards at each site approved the study protocol before the study began at that site. Written informed consent was provided by all participants before any study procedures were initiated. All of the participants met the DSM–IV (American Psychiatric Association, 1994) criteria for MDD without psychotic features as assessed using the Mini International Neuropsychiatric Interview (MINI; Sheehan et al, 1998). Baseline disease severity was assessed using the 17-item Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960) and the Clinical Global Impression–Severity (CGI–S) scale (Guy, 1976). At both the screening and second study visits, all study participants were required to meet the entry criteria of HRSD17 score ≥18 and CGI–S score ≥4, indicating at least moderate depression. In addition, participants must have had at least one other major depressive episode before the episode that was being experienced at the time of entry to the study.

Exclusion criteria: Reasons for exclusion from the study included the following: having a current and primary Axis I disorder other than MDD; anxiety disorder as a primary diagnosis within 1 year of entry to the study; treatment-resistant depression; serious suicidal risk; and serious medical illness.

Perahia 2009

Inclusion criteria: Patients were male and female outpatients of at least 18 years of age who met criteria for recurrent MDD as defined by the DSM-IV and confirmed via the MINI. Patients were recruited from 43 study centers in 5 European countries (France, Germany, Italy, Russia, and Sweden) and the United States. In order to be eligible for the study, patients had to have a HAM-D-17 score ≥ 18 and a CGI-S score ≥ 4 at the screening visit and the beginning of the acute phase and must have had at least 3 episodes of depression (including the presenting episode) within the past 5 years. Patients also had to have been in remission between these 3 episodes of depression (in order for DSMIV criteria for recurrent depression to be met) and had to have been stable and off antidepressant medication for at least 2 months prior to the onset of the presenting episode.

Exclusion criteria: Patients were not eligible to participate in the study if they met any of the following criteria: a current and primary Axis I disorder other than MDD, including but not limited to dysthymia; a previous diagnosis of bipolar disorder, schizophrenia, or other psychotic disorders; any anxiety disorder as a primary diagnosis within the past year; an Axis II disorder that in the judgment of the investigator would interfere with compliance with the study protocol; a DSM-IV–defined history of substance abuse or dependence within the past year, excluding nicotine and caffeine; a positive urine drug screen for any substances of abuse, including benzodiazepines; taking any excluded medications (which included most centrally acting medications such as antidepressants and antipsychotics) within 7 days prior to visit 2; treatment with a monoamine oxidase inhibitor within 14 days prior to study onset; and treatment with fluoxetine within 30 days prior to study onset. Patients who had a prior treatment history with duloxetine, who were judged to be at serious suicide risk, or who had had a serious medical illness likely to require hospitalization and/or the use of prohibited medications were also excluded, as were women who were breastfeeding or pregnant. Women of childbearing potential were required to use reliable methods of birth control.

Rapaport 2004

Inclusion criteria: Subjects (male or female, aged 18-81 years) had been diagnosed with major depressive disorder and had completed 8 weeks of randomized double-blind acute treatment with 10 to 20 mg/day of escitalopram, 20 to 40 mg/day of citalopram, or placebo. Patients entered the current continuation trial within 72 hours of completing one of the lead-in trials. To qualify for the lead-in trial, patients were required to have a minimum baseline Montgomery-Åsberg Depression Rating Scale (MADRS) score of 22 and to have met DSM-IV criteria for an ongoing major depressive episode of at least 4 weeks' duration. For both trials, the primary efficacy measure was the mean change from baseline to week 8 in MADRS score using the last observation carried forward (LOCF). One of the lead-in trials was a fixed-dose study in which both escitalopram and citalopram produced significant reductions in LOCF MADRS scores relative to placebo. In the second trial, a flexible-dose study, escitalopram and citalopram both produced significant reductions versus placebo in MADRS scores at week 8 for the observed cases data set but not for the LOCF data set (data on file, Forest Laboratories, Inc., New York, N.Y.).

Exclusion criteria: Exclusion criteria included any principal Axis I disorder other than major depressive disorder and a history of schizophrenia or any other psychotic disorder. In addition, patients who presented a suicide risk, scored at least 5 on MADRS item 10 (suicidality), or required concomitant psychotropic medication (with the exception of zolpidem for insomnia) were ineligible to enroll. Women of childbearing potential were not eligible if pregnant and were required to employ a reliable method of contraception.

Rickels 2010

Inclusion criteria: Male and female outpatients, 18 to 75 years of age, with a primary diagnosis of MDD using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (American Psychiatric Association, 1994) criteria, single or recurrent episode, without psychotic features, and who had symptoms for at least 30 days before screening, were eligible for study participation. The modified Mini-International Neuropsychiatric Interview 24 was used to indicate the primary diagnosis of MDD and any comorbid psychiatric disorders that may have been present, with confirmation by psychiatric interview. At screening and baseline, patients were also required to have a minimum HAM-D 17 total score of 20, score at least 2 on item 1 (depressed mood) of the HAM-D 17, and a Clinical Global Impression Severity (CGI-S) 25 score of at least 4 on a scale of 7 (1, normal and 7, extremely ill).

Exclusion criteria: Medical and psychiatric histories were obtained at screening. Patients with current comorbid substance use disorders were excluded; however, patients with comorbid generalized anxiety, panic, or social anxiety disorder were allowed to participate as long as MDD was the primary diagnosis (i.e., the comorbid disorder did not cause a higher degree of distress or impairment than MDD), based on the opinion of the investigator. Other exclusion criteria included treatment with desvenlafaxine at any time in the past, treatment with venlafaxine (IR or ER formulation) within 90 days, or known hypersensitivity to venlafaxine (IR or ER); risk of suicide based on clinical judgment; pregnant, breast-feeding, or planning to

become pregnant during the study; current (within 12 months from baseline) manic episodes, posttraumatic stress disorder, obsessive-compulsive disorder, or clinically important personality disorder; depression associated with an organic mental disorder due to a general medical condition or neurological disorder; history of a seizure disorder; or clinically important medical disease.

Robert 1995

Inclusion criteria: Depressed patients meeting the diagnostic criteria of DSM-III-R (American Psychiatric Association, 1987) with a score of at least 25 on the Montgomery and Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979) were included in the multicentre study.

Exclusion criteria: Patients whose depression had a duration of more than 3 months were excluded.

Rosenthal 2013

Inclusion criteria: Eligible patients included male and female adult outpatients (≥ 18 years) with a primary diagnosis of single-episode or recurrent MDD without psychotic features, based on criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Comorbid generalized anxiety, panic, or social anxiety disorders were allowed if MDD was the primary diagnosis. Eligible patients had depressive symptoms for at least 30 days before the screening visit, a 17-item Hamilton Depression Rating Scale ($HDRS_{17}$) total score ≥ 20, a HAM-D_{17} item 1 (depressed mood) score ≥ 2, and a Clinical Global Impressions-Severity of Illness scale (CGI-S) score ≥ 4 at screening and baseline visits.

Exclusion criteria: (CGI-S) score ≥ 4 at screening and baseline visits. Patients were excluded if they had been treated with desvenlafaxine at any time in the past or if they had a significant risk of suicide based on clinical judgment or an $HDRS_{17}$ item 3 (suicide) score greater than 3 at screening. Other major exclusion criteria included current comorbid substance use disorder, manic episode, posttraumatic stress disorder, obsessive-compulsive disorder, clinically important personality disorder (as assessed by the modified Mini-International Neuropsychiatric Interviews and a psychiatric interview), or clinically important medical disease.

Rouillon 2000

Inclusion criteria: Male and female patients, whether hospitalized or not, aged 18-70 years, who had a history of recurrent major depressive disorder (MDD) and a current major depressive episode without psychotic symptoms according to DSM-III-R (American Psychiatric Association, 1982) criteria, with a severity rating on the HDRS (21-item) (Hamilton, 1960) ≥ 18, and who signed an informed consent form, were entered into the study.

Exclusion criteria: Subjects were to be excluded from the study if they had any of the following diagnoses: mania, hypomania, dysthymia, depression secondary to schizophrenia or schizo-affective disorder, alcoholism or drug addiction. For patient safety, those with obvious suicidal intent were not included.

Patients were excluded from the study if they had treatment-resistant depression, cardiac rhythm disorders requiring an anti-arrhythmic treatment, kidney failure, past history of epilepsy, past history of serious allergic or toxic reaction to a drug, or life-threatening disorders. Abnormalities in clinical chemistry, hematology, or urinalysis at inclusion as well as pregnancy, lack of effective birth control, or breastfeeding were also reasons for exclusion from the study. Minor tranquillizers equivalent to ≤ 50 mg/day of oxazepam were allowed for the duration of the study:

Schmidt 2000

Inclusion criteria:

Patients were male or female outpatients, aged 18 to 80 years, who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for nonpsychotic major depression with a current episode duration of at least 4 weeks and disease severity of at least moderate intensity, confirmed by

interview with the Structured Clinical Interview for DSM-IV patient version (SCID-P) (modified 17-item Hamilton Rating Scale for Depression [HAM-D-17] score of ≥ 18 and a Clinical Global Impressions-Severity of Illness scale [CGI-S] score ≥ 4).

Exclusion criteria: Patients with a lifetime history of any psychotic disorder, bipolar mood disorder, or substance abuse disorder in the preceding year or current or recent anxiety disorder that was a primary focus of treatment were excluded. Patients were also excluded if they were previously non-responsive to an adequate course of fluoxetine antidepressant treatment or if their current episode was unresponsive to 2 or more adequate courses of antidepressant therapy. Patients received no form of psychotherapy directed toward their depression during the study other than good clinical care. Pregnant or lactating patients and patients with unstable medical conditions were also excluded from the protocol.

Shiovitz 2014

Inclusion criteria: Male and female outpatients 18 to 65 years of age were eligible to participate in the study if they met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for MDD with an ongoing depressive episode of at least four weeks' duration; the diagnosis was confirmed by the Mini International Neuropsychiatric Interview (MINI) 20 and a MADRS total score of 22 or greater. Patients were required to have normal physical examination results, clinical laboratory determinations, and electrocardiogram (ECG) findings, or abnormal results that were judged by the Investigator to be not clinically significant.

Exclusion criteria: Patients were excluded if they had been diagnosed with any DSM-IV-TR Axis I disorder other than MDD within six months of screening (comorbid generalized anxiety disorder, social anxiety disorder, and/or specific phobias were permitted), had a history of various psychiatric disorders (e.g., mania, depressive episode with psychotic features, obsessive-compulsive disorder, schizophrenia, borderline or antisocial personality disorder, cognitive disorder), or had substance abuse or dependence within six months of screening. Additional reasons for exclusion included the following: history of nonresponse to two or more adequate treatment trials with antidepressants; certain medical conditions (e.g., cardiovascular, pulmonary, hepatic, gastrointestinal, renal, endocrine, neurological, autoimmune, or infectious disease) that may have interfered with the conduct of the study or confounded interpretation of study results; history or ECG evidence of QTc prolongation or pulse rates or blood pressures outside of normal limits at screening; female patients of child-bearing potential who were pregnant, breastfeeding, or not currently using a medically acceptable method of contraception; and significant risk of suicide determined by the Investigator or information generated from the Columbia-Suicide Severity Rating Scale (C-SSRS), 21 suicide attempt within the past year, or a score of 5 or greater on MADRS Item 10 (Suicidal Thoughts).

Simon 2004

Inclusion criteria: Men and women were eligible for the study if they met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (American Psychiatric Association, 1994) criteria for MDD, with a 21-item Hamilton Rating Scale for Depression (HAM-D 21) (Hamilton, 1960) score 520 at pre-study and baseline visits and no greater than a 20% decrease in the HAM-D 21 score between these evaluations. Patients had to be at least 18 years old and to have had symptoms of depression for at least 1 month before study entry.

Exclusion criteria: Pregnant or breast-feeding women were excluded from the study. Also excluded were patients with myocardial infarction within the last 6 months, those who were acutely suicidal, and those with a history or presence of hepatic or renal disease, seizure disorder, psychotic disorder, or bipolar disorder. Prior use of venlafaxine was prohibited within 6 months of the screening visit. Use of investigational drugs, antipsychotic agents, or fluoxetine within 30 days, any other antidepressant within 14 days, or any sedative/hypnotic drug (except chloral hydrate and zolpidem tartrate, up to 2 nights per week) within 7 days of the screening visit and throughout the study was prohibited.

Stein 1998

Inclusion criteria: All patients had completed an acute treatment trial of amitriptyline (o.d. versus t.i.d.) lasting 6 weeks and were judged to be at least moderately improved. The larger sample from which these subjects were drawn and other aspects of methodology have been described in detail in Weise and associates (10).

Description in Weise et al (Arch Gen Psychiatry 1980 May;37(5):555-60)

All patients fulfilled the Feighner et al criteria for major depressive disorder that overlap with those of the DSM-III. Only patients having at least a Raskin Depression score of "8" and a Hamilton Depression Scale (HDS) (21-item scale) of "18" entered the study.

Exclusion criteria (described in *Weise et al, 1980*):

Excluded were patients under 18 years and over 70 years of age, and patients with strong sociopathic trends, alcoholism, organic brain syndromes, or evidence of schizophrenia. Patients receiving therapeutic doses of amitriptyline for at least four weeks prior to the study were not accepted. Also excluded were patients with cardiac or thyroid disorders, or with disorders requiring sedatives or analgesics; subjects with a positive history of glaucoma, urinary retention, or prostatic hypertrophy; those requiring guanethidine, and pregnant or lactating women.

Thase 2001

Inclusion criteria: Patients (aged 18 years and older) were potentially eligible for participation if they met criteria for a principal DSM-IV diagnosis of major depressive disorder and had at least 1 of 2 risk indicators: (1) recurrent subtype, with at least 1 prior episode within the past 5 years, or (2) chronic subtype, with a current episode duration of ≥ 2 years. Diagnoses were based on a clinical interview conducted by a study psychiatrist and recorded using a checklist of DSM-IV criteria. In most cases, structured diagnostic interviews (e.g., the Schedule for Affective Disorders and Schizophrenia or the Structured Clinical Interviews for DSM-IV) were not utilized to confirm eligibility. Current episode duration and lifetime history of prior depressive episodes also were determined during this interview. Potentially eligible patients had to be in reasonably good physical health, not have abused drugs or alcohol for at least 3 months before enrolment, and provide explicit written informed consent. Patients had to agree not to begin psychotherapy during the study, although they were permitted to remain in ongoing psychotherapy (minimum duration = 3 months). Female patients also had to agree not to become pregnant during the study (i.e., for up to 1 year) and, if sexually active and capable of becoming pregnant, to use a proven form of contraception (e.g., oral contraceptives or double barrier methods).

Exclusion criteria:

Patients could not enter the study if they had received monoamine oxidase inhibitors within the previous 14 days, selective serotonin reuptake inhibitors other than fluoxetine within 7 days, fluoxetine or any investigational drug within 30 days, or any other psychotropic drugs within 7 days. Patients were not eligible for study participation if they had ever taken mirtazapine or if they had failed an adequate trial (at least 4 weeks of therapy at maximally effective doses) of any approved antidepressant in the current episode. The following concomitant conditions led to patient exclusion: anorexia or bulimia nervosa, obsessive-compulsive disorder, schizophrenia, dementia, or bipolar disorder. Additionally, patients judged to have severe borderline, antisocial, or schizoid personality disorders were excluded. Other psychiatric comorbidities (e.g., panic disorder, generalized anxiety disorder, or avoidant personality disorder) were not exclusion criteria as long as the depressive disorder was considered to be the principal (i.e., clinically predominant) diagnosis.

Versiani 1999

Inclusion criteria: Patients aged 18 to 65 years with a diagnosis of acute recurrence of DSM-III-R major depressive disorder attending outpatient clinics or having recently been hospitalized (within 2 weeks) were eligible for inclusion in this study. Patients were required to have a total score on the 21-item HAM-D of ≥ 18

points. Following the initial 6-week treatment period, those patients responding to treatment with reboxetine were eligible to participate in the long-term phase of the study.

Exclusion criteria: Patients with evidence of coexisting psychotic features (DSM-III-R) and those with evidence of chronic depression (based on 3 of the Composite Diagnostic Evaluation of Depressive Disorders [CODE-DD] variables: acute or subacute onset and prolonged duration) were not eligible for inclusion. Patients were also excluded if they were experiencing their first episode of major depression at the time of screening, if they had a history of major depression associated with an endocrinologic disorder, or if they had received electroconvulsive therapy in the previous 6 months. Those with a history of seizures, serious brain injury, or evidence of clinically significant hemopoietic or cardiovascular disease, urinary retention, or glaucoma were also excluded.

Weihs 2002

Inclusion criteria: Men and women at least 18 years old and in generally good health were eligible for this multicenter, parallel-group, randomized, double-blind, fixed-dose, placebo-controlled study (Protocol AK1A4004). Patients must have been diagnosed with moderate to severe, recurrent major depression based on Diagnostic and Statistical Manual-IV (DSM-IV; American Psychiatric Association 1994) criteria and must have had a minimum score of 18 on the 21-item Hamilton Depression Scale (HAMD) (Hamilton 1960, 1967) at screening (day 6) and baseline (day 0). The patient's current depressive episode must have had a duration of 8 weeks to 24 months and must have been preceded by at least one other episode within the past 60 months. Patients must also have had at least 6 months of euthymia between the current depressive episode and their previous episode to ensure that the current episode was separate and distinct.

Exclusion criteria: Patients were excluded from the study if they had a known predisposition to seizures or were receiving medications that lowered the seizure threshold; had a history or current diagnosis of anorexia or bulimia; had a DSM-IV (American Psychiatric Association 1994) Axis II diagnosis suggesting a propensity for non-compliance or non-responsiveness to pharmacotherapy for depression; were pregnant, lactating, or did not agree to avoid pregnancy during the study; had a history of alcohol or substance abuse or dependence within the past year; had used any psychoactive drug within 1 week of study drug treatment (2 weeks for monoamine oxidase inhibitors or protriptyline, 4 weeks for fluoxetine or any investigational drug); had a history of treatment with bupropion within the past year or had previously received bupropion in a clinical study; or were actively suicidal.

Durgam 2019

Inclusion criteria: The study included male and female outpatients (≥ 18 to ≤ 70 years) who met the following eligibility criteria: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for MDD (APA, 2013), confirmed by a Mini International Neuropsychiatric Interview; ongoing major depressive episode (duration ≥ 8 weeks to ≤ 18 months); ≥ 3 lifetime depressive episodes (including current episode), with 2 episodes (including current) occurring within the past 5 years; MADRS total score ≥ 26; and body mass index between ≥ 18 and ≤ 40 kg/m^2.

Exclusion criteria: Patients who met any of the following criteria were excluded from study participation: DSM-5 Axis I diagnosis of a disorder other than MDD within 6 months of screening (secondary diagnoses of comorbid generalized anxiety disorder, social anxiety disorder, and/or specific phobias were allowed); history of mania, psychotic disorder, panic disorder, obsessive–compulsive disorder, bulimia or anorexia nervosa (past 5 years), borderline or antisocial personality disorder, or neurocognitive disorder; alcohol or other substance abuse disorder (past 6 months); nonresponse to adequate treatment with ≥ 2 antidepressants (i.e., 8-week duration at recommended dose) during the current episode; and suicide risk defined as suicide attempt (past 12 months), MADRS Item 10 score ≥ 5, or determined by the investigator based on the psychiatric interview or information collected in the ColumbiaSuicide Severity Rating Scale (C-SSRS; Posner et al., 2011). Concomitant treatment with psychoactive medications was prohibited, except for medications for insomnia.

Durgam 2018

Inclusion criteria: Men and women (18 – 70 years, inclusive) with a Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision (DSM-IV-TR) diagnosis of MDD (American Psychiatric Association, 2000) were included in the study. Patients had an ongoing major depressive episode (≥ 8 weeks to ≤ 18 months); at least three lifetime depressive episodes (including current episode) and two episodes within 5 years before screening (including the current episode); MADRS total score of at least 26; and BMI of at least 18 and up to 40 kg/m^2.

Exclusion criteria: Patients were excluded if they had a current DSM-IV-TR Axis I disorder other than MDD within 6 months before screening (comorbid generalized anxiety disorder, social anxiety disorder, and/or specific phobias were allowed); history of manic, psychotic, obsessive – compulsive, personality, and/or cognitive disorder(s); substance abuse or dependence within 6 months before screening; suicide risk, based on investigator judgment, suicide attempt within the past year, MADRS suicidal thoughts item score of at least 5, and/or Columbia-Suicide Severity Rating Scale (C-SSRS) findings; nonresponse to at least two antidepressants after at least 8 weeks of treatment at approved recommended doses; and any condition that could interfere with study conduct, confound interpretation of study results, or endanger patient well-being. Concomitant use of medications with psychoactive effects or strong cytochrome P450 effects was prohibited; medications for insomnia (e.g. eszopiclone, zopiclone, zaleplon, zolpidem) were allowed as needed.

Thase 2022

Inclusion criteria: Eligible participants included men and women aged 18 – 75 years with a primary diagnosis of recurrent MDD (Montgomery-Åsberg Depression Rating Scale [MADRS] score ≥ 26 at screening and baseline I) and a duration of current major depressive episodes (MDEs) between 8 weeks and 18 months. Participants must also have had a history of at least 2 previous MDEs before the current episode.

Exclusion criteria: Study participants were excluded if they had a clinically significant neurological, comorbid, or Axis II disorder; were considered to be at significant risk of suicide; or if current depressive symptoms were resistant to vortioxetine or 2 antidepressant treatments for at least 6 weeks.

Reimherr 1998

Inclusion criteria: The study subjects were male and female outpatients, 18–65 years of age, who met the DSM-III-R criteria for major depression with a duration of at least 1 month. All patients had a modified 17-item Hamilton Depression Rating Scale (17) score of at least 16.

Exclusion criteria: Patients with type I bipolar disorder were excluded from the study, but depressed patients with type II bipolar disorder could be included if they met other entry criteria

Segal 2010

Inclusion criteria: Inclusion criteria were: (1) diagnosis of Major Depressive Disorder (MDD) according to DSM-IV criteria, (2) a score of ≥ 16 on the Hamilton Depression Rating Scale (HRSD-17), (3) ≥ 2 previous episodes of MDD [to ensure that those randomized would have a minimum of 3 past episodes], (4) between 18 and 65 years of age and (5) English speaking and the ability to provide informed consent.

Exclusion criteria: Exclusion criteria were: (1) a current diagnosis of Bipolar Disorder, Substance Abuse Disorder, Schizophrenia or Borderline Personality Disorder, (2) a trial of ECT within the past six months (3) depression secondary to a concurrent medical disorder, (4) current or planned pregnancy within the 6 months of acute phase treatment, (5) current practice of meditation more than once per week or yoga more than twice per week.

Stewart 1997

Inclusion criteria: Patients asked to participate were judged at least much improved after an acute antidepressant trial with imipramine or phenelzine at the Depression Evaluation Service, an outpatient research clinic of the New York State Psychiatric Institute. Before acute treatment, patients had been diagnosed as depressed (i.e., major depression, dysthymia, or both) by DSM-III criteria and as having definite or probable atypical depression according to Columbia University criteria (13). All had been depressed at least 2 years, had responded to an acute trial of imipramine or phenelzine, and had maintained their remission for at least 6 months. Both acute response and maintenance of benefit were defined by the treating psychiatrist's assessment on the Clinical Global Impression (CGI) (22) global improvement scale. Patients' positive response to acute treatment was defined as a CGI rating of much improved or very much improved, relative to their depressed baseline state, at the end of a 6-week acute trial.

Maintenance of response was defined as CGI ratings of much improved or very much improved at each of six monthly follow-up visits. Thus, patients were essentially free of depressive symptoms for 6 months. After complete description of the study to the subjects, written informed consent was obtained. Columbia University criteria for definite atypical depression (13) were incorporated into DSM-IV and include distinct reactivity of mood plus two of four associated features (hyperphagia, hypersomnia, leaden paralysis, rejection sensitivity). Criteria for probable atypical depression required mood reactivity plus one of the four associated features. All patients were between ages 18 and 65 and were physically healthy. Patients who initially responded to phenelzine were on a low tyramine diet throughout. Baseline measures included the Structured Clinical Interview for DSM-III (23), the Hamilton Depression Rating Scale (24), CGI, and the 90 item SCL-90 (25). Before acute treatment, patients were also evaluated for percent of time depressed as an adult, age at onset of first depression, and months since last 3 months of well-being. Presence or absence of chronic dysphoria, defined as onset of depressed mood before age 25, no 6 months of well-being since onset, and depressed at least 50% of the adult life, was also assessed. Patients who were rated much improved or very much improved during monthly continuation visits were randomly assigned after 6 months to continue their same medication or be switched to placebo. For patients who were switched to placebo, their active medication was tapered over 2 weeks, while patients assigned to active medication maintained their continuation dose. After randomization and for the remainder of the study, patients and doctors were blind to treatment. Patients and doctors knew, however, whether the patient was in the phenelzine or imipramine arm of the study.

Exclusion criteria: *[Not explicitly stated.]* All patients were between ages 18 and 65 and were physically healthy.

Supplement to Results

Supplementary Table 1. Prevalence of the exclusion criteria and other characteristics of the Finnish (N=73,720) and Swedish cohorts (N=135,092).

Characteristics	**Finland, % (N)**	**Sweden, % (N)**
Women (%)	50,041 (67.9%)	85,683 (63.4%)
Men (%)	23,679 (32.1%)	49,409 (36.6%)
Age (mean, SD), years	40.2 (12.5)	38.5 (12.8)
First-time secondary care diagnosis of depression	61,430 (83.3)	117,110 (86.7)
Exclusion criteria		
Serious somatic disease, broad definition	31,409 (42.6)	60,936 (45.1)
Serious somatic disease, narrow definition	13,911 (18.9)	21,653 (16.0)
Other psychiatric disorders	8772 (11.9)	20,286 (15.0)
Substance use disorder	4136 (5.6)	10,270 (7.6)
Pregnancy or breastfeeding	2366 (3.2)	5301 (3.9)
History of suicide attempt	2064 (2.8)	4863 (3.6)
Intellectual disability	84 (0.1)	417 (0.3)
History of ECT or other neuromodulation	43 (0.1)	336 (0.2)

ECT = electroconvulsive therapy; SD = standard deviation

Supplementary Table 2. Prevalence of the most frequently used antidepressants and antidepressant classes during the stabilization phase in the Finnish (N=73,720) and Swedish cohorts (N=135,092) in order of frequence.

	Finnish cohort			**Swedish cohort**	
Drug class/drug	**Ineligible, n=24,677**	**Eligible, n=49,043**	**Drug class/drug**	**Ineligible, n=47,695**	**Eligible, n=87,397**
SSRI in total	16,650 (67.5%)	35,602 (72.6%)	**SSRI in total**	35,415 (74.3%)	71,826 (82.2%)
Escitalopram	7177 (29.1%)	16,731 (34.1%)	Sertraline	Sertraline 16,441 (34.5%)	Sertraline 31,748 (36.3%)
Citalopram	5013 (20.3%)	11,113 (22.7%)	Citalopram	7825 (16.4%)	21,503 (24.6%)
Fluoxetine	1380 (5.6%)	2588 (5.3%)	Escitalopram	6426 (13.5%)	12,000 (13.7%)
SNRI in total	3249 (13.2%)	SNRI 5721 (11.7%)	**Mirtazapine**	5036 (10.6%)	6938 (7.9%)
Mirtazapine	2959 (12.0%)	5290 (10.8%)	**SNRI in total**	4378 (9.2%)	6128 (7.0%)
Other	1522 (6.2%)	2124 (4.3%)	**Other**	2322 (4.9%)	1946 (2.2%)
TCA in total	297 (1.2%)	TCA 306 (0.6%)	**TCA in total**	544 (1.1%)	559 (0.6%)

SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin and noradrenaline reuptake inhibitor; TCA = tricyclic antidepressant

Sensitivity Analyses

Supplementary Table 3. Sensitivity analysis of the risk of the primary outcome in individuals ineligible (≥ 1 exclusion criteria) vs eligible (without any exclusion criterion) to randomized clinical trials in individuals using >15mg dose of mirtazapine.

	Finland		Sweden	
	N of users	**HR (95% CI)**	**N of users**	**HR (95% CI)**
6-month follow-up period				
Mirtazapine >15mg	6034	3.22 (2.17–4.77)	9426	3.55 (2.55–4.93)
Any SSRI	52,252	2.27 (1.95–2.64)	107,241	2.21 (1.98–2.48o)
9-month follow-up period				
Mirtazapine >15mg,	6034	3.11 (2.16–4.48)	9426	3.64 (2.68–4.95)
Any SSRI	52,252	2.31 (2.01–2.65)	107,241	2.26 (2.03–2.50)

CI = Confidence interval; HR = Hazard ratio

Supplementary Table 4. Sensitivity analysis of the 9-month risk of primary and secondary outcomes in individuals ineligible (≥ 1 exclusion criteria) vs eligible (without any exclusion criterion) to randomized clinical trials in the Finnish (N=73,720) and Swedish (N=135,092).

	Finland		Sweden	
Outcomes	**Number of events**	**HR (95% CI)**	**Number of events**	**HR (95% CI)**
Composite primary outcome	1163	2.43 (2.17, 2.73)	2028	2.60 (2.38, 2.84)
All-cause mortality	65	2.83 (1.73, 4.64)	77	2.99 (1.89, 4.73)
Psychiatric hospitalization	877	2.25 (1.97, 2.57)	1618	2.73 (2.47, 3.01)
Suicide attempt or death	260	3.12 (2.43, 4.00)	499	2.12 (1.78, 2.53)
Secondary outcomes				
Discontinuation, switch, or augmentation	43,527	1.02 (1.00, 1.04)	71,041	1.11 (1.10, 1.13)
Sick leave	3458	0.95 (0.89, 1.02)	3948	1.18 (1.11, 1.26)

CI = Confidence interval; HR = Hazard ratio

Supplementary Table 5. Sensitivity analysis of the 9-month risks of the primary outcome (all-cause mortality and/or hospitalization due to suicide attempt and/or for any psychiatric reason) in the population of individuals remaining after applying each specific exclusion criteria (eligible group) (Finland N=73,720, Sweden N=135,092).

	Finland		Sweden	
Exclusion criteria	**N (%)**	**HR (95% CI)**	**N (%)**	**HR (95% CI)**
Substance use disorder	4073 (5.5%)	5.18 (4.50, 5.96)	10,270 (7.6%)	5.28 (4.79, 5.81)
Intellectual disability	79 (0.1%)	3.24 (1.21, 8.65)	417 (0.3%)	1.98 (1.12, 3.49)
Other psychiatric disorders	8651 (11.7%)	2.02 (1.75, 2.32)	20,286 (15.0%)	2.19 (1.98, 2.41)
Pregnancy or breastfeeding	2375 (3.2%)	0.88 (0.63, 1.24)	5301 (3.9%)	0.70 (0.54, 0.91)
History of suicide attempt	2050 (2.8%)	6.00 (5.08, 7.10)	4863 (3.6%)	5.15 (4.56, 5.82)
Serious somatic disease, broad definition	31,208 (42.3%)	1.32 (1.18, 1.48)	60,936 (45.1%)	1.15 (1.05, 1.25)
Serious osmatic disease, narrow definition	13,814 (18.7%)	1.47 (1.29, 1.67)	21,653 (16.0%)	1.31 (1.18, 1.46)
Neuromodulation	40 (0.1%)	3.17 (0.79, 12.7)	336 (0.2%)	4.98 (3.33, 7.45)

CI = Confidence interval; HR = adjusted Hazard ratio

Supplementary Table 6. Sensitivity analysis applying broad criteria for serious somatic disorder on the risk of primary and secondary outcomes in individuals ineligible (≥ 1 exclusion criteria) vs eligible (without any exclusion criterion) to randomized clinical trials in the Finnish (N=73,720) and Swedish (N=135,092) cohorts.

	Finland		Sweden	
Outcomes	**Number of events**	**HR (95% CI)**	**Number of events**	**HR (95% CI)**
Composite primary outcome	999	2.06 (1.80, 2.36)	1731	2.02 (1.82, 2.24)
All-cause mortality	52	1.60 (0.91, 2.82)	61	1.60 (0.94, 2.74)
Psychiatric hospitalization	757	2.04 (1.75, 2.38)	1374	2.09 (1.86, 2.35)
Suicide attempt or death	219	2.28 (1.71, 3.06)	432	1.92 (1.56, 2.36)
Secondary outcomes				
Discontinuation, switch, or augmentation	35,127	1.03 (1.01, 1.05)	55,248	1.09 (1.07, 1.10)
Sick leave	2777	1.02 (0.94, 1.10)	3186	1.29 (1.20, 1.38)

CI = Confidence interval; HR = adjusted Hazard ratio

Supplementary Table 7. Sensitivity analysis not censoring to treatment change on the risk of primary outcome and the secondary outcome of sick leave in individuals ineligible (≥ 1 exclusion criteria) vs eligible (without any exclusion criterion) to randomized clinical trials in the Finnish (N=73,720) and Swedish (N=135,092) cohorts.

	Finland		Sweden	
Outcomes	**Number of events**	**HR (95% CI)**	**Number of events**	**HR (95% CI)**
Composite primary outcome	1503	2.54 (2.30, 2.82)	2588	2.58 (2.38, 2.78)
All-cause mortality	136	3.53 (2.49, 5.01)	152	2.81 (2.03, 3.89)
Psychiatric hospitalization	1143	2.38 (2.11, 2.67)	2131	2.60 (2.38, 2.83)
Suicide attempt or death	325	2.95 (2.37, 3.69)	650	2.09 (1.79, 2.44)
Secondary outcomes				
Sick leave	3668	0.98 (0.92, 1.06)	4136	1.22 (1.14, 1.30)

CI = Confidence interval; HR = adjusted Hazard ratio

RECORD-PE Reporting Checklist

The RECORD statement for pharmacoepidemiology (RECORD-PE) checklist of items, extended from the STROBE and RECORD statements, which should be reported in non-interventional pharmacoepidemiologic studies using routinely collected health care data.[6]

Item No	STROBE items	RECORD items	RECORD-PE items	Page No
Title and abstract				
1	(a) Indicate the study's design with a commonly used term in the title or the abstract. (b) Provide in the abstract an informative and balanced summary of what was done and what was found.	1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. 1.2: If applicable, the geographical region and timeframe within which the study took place should be reported in the title or abstract. 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	—	1 - 3
Introduction				
Background rationale				
2	Explain the scientific background and rationale for the investigation being reported.	—	—	4
Objectives				
3	State specific objectives, including any prespecified hypotheses.	—	—	5
Methods				
Study design				
4	Present key elements of study design early in the paper.	—	4.a: Include details of the specific study design (and its features) and report the use of multiple designs if used. 4.b: The use of a diagram(s) is recommended to illustrate key aspects of the study design(s), including exposure, washout, lag and observation periods, and covariate definitions as relevant.	5
Setting				
5	Describe the setting, locations, and relevant dates,	—	—	5-6

	including periods of recruitment, exposure, follow-up, and data collection.			
Participants				
6	(a) Cohort study—give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. Case-control study—give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. Cross sectional study—give the eligibility criteria, and the sources and methods of selection of participants. (b) Cohort study—for matched studies, give matching criteria and number of exposed and unexposed. Case-control study—for matched studies, give matching criteria and the number of controls per case.	6.1: The methods of study population selection (such as codes or algorithms used to identify participants) should be listed in detail. If this is not possible, an explanation should be provided. 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	6.1.a: Describe the study entry criteria and the order in which these criteria were applied to identify the study population. Specify whether only users with a specific indication were included and whether patients were allowed to enter the study population once or if multiple entries were permitted. See explanatory document for guidance related to matched designs.	5-6
Variables				
7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	7.1.a: Describe how the drug exposure definition was developed. 7.1.b: Specify the data sources from which drug exposure information for individuals was obtained. 7.1.c: Describe the time window(s) during which an individual is considered exposed to the drug(s). The rationale for selecting a particular time window should be provided. The extent of potential left truncation or left censoring should be specified. 7.1.d: Justify how events are attributed to current, prior, ever, or cumulative drug exposure. 7.1.e: When examining drug dose and risk attribution, describe how current,	6-7

			historical or time on therapy are considered. 7.1.f: Use of any comparator groups should be outlined and justified. 7.1.g: Outline the approach used to handle individuals with more than one relevant drug exposure during the study period.	
Data sources/measurement				
8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.	—	8.a: Describe the healthcare system and mechanisms for generating the drug exposure records. Specify the care setting in which the drug(s) of interest was prescribed.	6-7
Bias				
9	Describe any efforts to address potential sources of bias.	—	—	7
Study size				
10	Explain how the study size was arrived at.	—	—	5-7
Quantitative variables				
11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why.	—	—	6-7
Statistical methods				
12	(a) Describe all statistical methods, including those used to control for confounding. (b) Describe any methods used to examine subgroups and interactions. (c) Explain how missing data were addressed. (d) Cohort study—if applicable, explain how loss to follow-up was addressed. Case-control study—if applicable, explain how matching of cases and controls was addressed. Cross sectional study—if applicable, describe analytical methods taking account of sampling strategy. (e) Describe any sensitivity analyses.	—	12.1.a: Describe the methods used to evaluate whether the assumptions have been met. 12.1.b: Describe and justify the use of multiple designs, design features, or analytical approaches.	6-8
Data access and cleaning methods				
12	—	12.1: Authors should describe the extent to which the investigators had access to the database population	—	6

		used to create the study population. 12.2: Authors should provide information on the data cleaning methods used in the study.		
Linkage				
12	—	12.3: State whether the study included person level, institutional level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	—	6
Results				
Participants				
13	(a) Report the numbers of individuals at each stage of the study (eg, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed). (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram.	13.1: Describe in detail the selection of the individuals included in the study (that is, study population selection) including filtering based on data quality, data availability, and linkage. The selection of included individuals can be described in the text or by means of the study flow diagram.	—	8
Descriptive data				
14	(a) Give characteristics of study participants (eg, demographic, clinical, social) and information on exposures and potential confounders. (b) Indicate the number of participants with missing data for each variable of interest. (c) Cohort study—summarise follow-up time (eg, average and total amount).	—	—	8-9; Table 1
Outcome data				
15	Cohort study—report numbers of outcome events or summary measures over time. Case-control study—report numbers in each exposure category, or summary measures of exposure. Cross sectional study—report numbers of outcome events or summary measures.	—	—	8-10, Tables 2 & 3
Main results				
16	(a) Give unadjusted estimates and, if applicable,	—	—	8-10, Tables

	confounder adjusted estimates and their precision (eg, 95% confidence intervals). Make clear which confounders were adjusted for and why they were included. (b) Report category boundaries when continuous variables are categorised. (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.			3 & 4 and Figures 1 & 2
Other analyses				
17	Report other analyses done—eg, analyses of subgroups and interactions, and sensitivity analyses.	—	—	10, Table 5
Discussion				
Key results				
18	Summarise key results with reference to study objectives.	—	—	11-12
Limitations				
19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	19.1.a: Describe the degree to which the chosen database(s) adequately captures the drug exposure(s) of interest.	12
Interpretation				
20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	—	20.a: Discuss the potential for confounding by indication, contraindication or disease severity or selection bias (healthy adherer/sick stopper) as alternative explanations for the study findings when relevant. **[A: Original text indicated this item was RECORD (ie, not RECORD-PE)?]**	11-12
Generalisability				
21	Discuss the generalisability (external validity) of the study results.	—	—	11-12
Other information				
Funding				
22	Give the source of funding and the role of the funders for the present study and, if	—	—	13

	applicable, for the original study on which the present article is based.			
Accessibility of protocol, raw data, and programming code				
22	—	22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	—	13

RECORD=reporting of studies conducted using observational routinely collected data; RECORD-PE=RECORD for pharmacoepidemiological research; STROBE=strengthening the reporting of observational studies in epidemiology.

References

1. Kishi T, Ikuta T, Sakuma K, et al. Antidepressants for the treatment of adults with major depressive disorder in the maintenance phase: a systematic review and network meta-analysis. *Mol Psychiatry*. 2023;28(1):402-409. doi:10.1038/s41380-022-01824-z

2. Shinohara K, Efthimiou O, Ostinelli EG, et al. Comparative efficacy and acceptability of antidepressants in the long-term treatment of major depression: protocol for a systematic review and networkmeta-analysis. *BMJ Open*. 2019;9(5):e027574. doi:10.1136/bmjopen-2018-027574

3. World Health Organization. International Classification of Diseases (ICD-10). 2010. Accessed April 21, 2020. https://icd.who.int/browse10/2010/en

4. Tanskanen A, Taipale H, Koponen M, et al. From prescription drug purchases to drug use periods – a second generation method (PRE2DUP). *BMC medical informatics and decision making*. 2015;15:21. doi:10.1186/s12911-015-0140-z

5. Taipale H, Tanskanen A, Koponen M, Tolppanen AMM, Tiihonen J, Hartikainen S. Agreement between PRE2DUP register data modeling method and comprehensive drug use interview among older persons. *Clinical Epidemiology*. 2016;8:363-371. doi:10.2147/CLEP.S116160

6. Langan SM, Schmidt SA, Wing K, et al. The reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE). *BMJ*. 2018;363:k3532. doi:10.1136/bmj.k3532