Effect and safety of discontinuation vs continuous intake of antidepressants in patients with anxiety and depression. (Literature review with meta-analysis)

Effect en veiligheid van stoppen versus continue inname van antidepressiva bij depressie/angst (literatuuronderzoek met metaanalyse).

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1. Abstract: (Nederlands)

Context: Antidepressiva worden meestal voorgeschreven voor depressie, maar ook voor andere indicaties, bijvoorbeeld angst. Het gebruik van antidepressiva is toegenomen voornamelijk voor de behandeling van depressie. Er is geen duidelijkheid in de richtlijnen met betrekking tot de duur van de behandeling na remissie. Eerdere reviews vergeleken het stoppen met antidepressiva versus het voortzetten ervan bij personen met angst of depressie die stabiel zijn en waarbij de behandeling na remissie minstens 6 maanden was. Deze studies geven geen duidelijk antwoord op de vraag of de stopzetting haalbaar en veilig is. Het doel van onze review is om te kijken naar de studies die antidepressiva stoppen bij personen met (stabiele) depressie of angst waarbij antidepressiva korter dan 6 maand gegeven werd versus antidepressiva doorgeven.

Onderzoeksvraag: Wat is de haalbaarheid en de veiligheid van stoppen van antidepressiva minder dan zes maand na remissie bij personen met depressie of angst die stabiel zijn versus doorgeven van antidepressiva?

Methode: Wij hebben een review met meta-analyse uitgevoerd van 26 RCT's"met een placebo-arm. Deze studies vergeleken antidepressiva stoppen bij personen met (stabiele) depressie of angst waarbij antidepressiva gedurende een periode van 3 tot 6 maanden gegeven werd versus antidepressiva doorgeven. Stopzetting van antidepressiva vond plaats tijdens de 'voortgezette fase' (continueringsfase), die gericht is op het voorkomen van terugval (relapse), of tijdens 'onderhoudsfase', die gericht is op het voorkomen van recidief (recurrence) na een periode van herstel.

Resultaten: 26 studies meldden stopzetting van antidepressiva. Maar geen van deze studies rapporteerde een succesvol stopzettingspercentage als primaire uitkomst. Deze studies waren voornamelijk opgezet om te onderbouwen dat voortzetting van antidepressiva gedurende 6 maanden beter was dan 3 maanden in termen van terugvalpreventie. Stoppen van antidepressiva kan leiden tot verergering van ontwenningsverschijnselen (OR 7.23, 95% CI 3.24-16.15 , 264 deelnemers, 1 studie), angstsymptomen (MD 1.86, 95% CI 1.32-2.40, 1915 deelnemers, 7 studies) en depressieve symptomen (MD 0.68, 95% CI 0.30-1.06; 1530 deelnemers, 7 studies) in vergelijking met het voortzetten van antidepressiva. De kwaliteit van leven is beter in de antidepressiva groep dan in de stopzettingsgroep (MD 0.50, 95% CI 0.37-0.62, 5269 deelnemers, 6 studies). Er is geen significant verschil in de stopzettingsgroep wat betreft bijwerkingen (OR 0.93, 95% CI 0.81-1.08, 3255 deelnemers, 10 studies) vergeleken met voortzetting van antidepressiva. Er is onduidelijkheid tussen relaps van depressie en dervingssymtomen in veel studies onder andere ten gevolg van abrupt stoppen van antidepressiva.

Conclusies: Deze nieuwe review (met meta-analyse) biedt onvoldoende bewijs om te suggereren dat stopzetting van antidepressiva veilig en effectief is in vergelijking met voortzetting na remissie bij personen die antidepressiva hebben gebruikt gedurende een periode van 3 tot 6 maanden na remissie. Daarom is het zonder begeleiding abrupt staken van antidepressiva na 3-6 maanden stabilisatie waarschijnlijk geen haalbare aanpak. Er is behoefte aan betrouwbare en specifieke studies gericht op verschillende stopzettingsstrategieën met succesvolle stopzetting als primair eindpunt en een duidelijk onderscheid tussen terugval en dervingsymptomen in toekomstig onderzoek.

Abstract :(English)

Background: Antidepressants are usually prescribed for depression but also for other indications e.g. anxiety. The use of anti-depressives is mainly increased by long term use of antidepressants. There is no evidence in guidelines regarding treatment duration after remission. Previous reviews compared discontinuation with continuation of antidepressants six months after remission but could not provide any concrete conclusion. Therefore, the aim of this new review (with meta-analysis) is to assess what is effectiveness and safety of approaches for discontinuation versus continuation of long-term antidepressant use for depression and anxiety disorders in adults who have been taking them for a period ranging from 3 to 6 months after remission.

Method: All 26 studies were RCTs with a placebo arm; All 26 studies compared discontinuation with continuation of antidepressants and discontinuation of antidepressant occurred during "continuation “treatment or “maintenance" treatment (as described by study authors in introduction) after stabilization. (Treatment duration with antidepressants is 12-24 weeks before randomization to achieve stabilization/remission).

Findings: Twenty-six studies reported discontinuation of antidepressant. But none of these studies reported successful discontinuation rate as a primary outcome. These studies were mainly designed to substantiate that continuation of AD for 6 months was better than 3 months in terms of relapse prevention. Discontinuation can increase withdrawal symptoms (OR 7.23, 95% CI 3.24 to 16.15 ,264 participants, 1 study), anxiety symptoms (MD 1.86, 95% CI 1.32 to 2.40 ,1915 participants, 7 studies), depressive symptoms (MD 0.68, 95% CI 0.30 to 1.06; 1530 participants, 7 studies) compared to continuation of antidepressants. Quality of life is better in continuation group than discontinuation group (MD 0.50, 95% CI 0.37 to 0.62 ,5269 participants, 6 studies). There is no significant difference in group with discontinuation for adverse events (odds ratio (OR) 0.93 (95% CI 0.83- 1.08), 3255 participants, 10 studies) compared to continuation of antidepressants. There is ambiguity between relapse of depression and withdrawal symptoms in many studies mainly due to abrupt discontinuation of antidepressants.

Interpretation: This new review (with meta-analysis) provides insufficient evidence to suggest that discontinuation of antidepressants is safe and effective compared to continuation after remission in individuals who have taken antidepressants for a period of 3 to 6 months after remission. Therefore, unsupervised abrupt discontinuation after 3-6 months of stabilization is probably not a viable approach. In future research there is a need for reliable studies with specific focus on different discontinuation strategies with successful discontinuation as the primary endpoint and a clear distinction between relapse and withdrawal symptoms.

Table of contents

1. **Abstract** 2
2. **Introduction** 6
   Why it is important to do the review 7
   PICO 7
3. **Method** 8
   - 3.1 Search method 8
   - 3.2 Selection of Studies 8
   - 3.3 Data extraction and management 8
   - 3.4 Main planned comparisons 8
   - 3.5 Assessment of risk of bias in included studies 8
   - 3.6 Measures of treatment effect 9
   - 3.7 Unit of analysis issues 9
4. **Results** 9
   - 4.1.1 Included studie s 9
   - 4.1.2 Design 10
   - 4.1.3 Aims of studies 10
   - 4.1.4 Setting 10
   - 4.1.5 Sample size 11
   - 4.1.6 Indication for antidepressant 11
   - 4.1.7 Duration 11
   - 4.1.8 Type 12
   - 4.1.9 Severity of depressive disorder/anxiety disorder at the moment of randomization 12
   - 4.2 Outcome measures 12
   - 4.2.1 Discontinuation Rate 12
   - 4.2.2 Withdrawal symptoms 12
   - 4.2.3 Adverse events 12
   - 4.2.4 Depressive symptoms (as defined by study authors) 13
   - 4.2.5 Anxiety symptoms 14
   - 4.2.6 Quality of life: 14
   - 4.3 Funding 14
   - 4.4 Exclusion criteria 14
   - 4.5 Excluded studies 14
   - 4.6 Risk of bias in included studies 14
   - 4.6.1 Allocation 15
     - sequence generation 15
     - Allocation concealment 15
   - 4.6.2 Blinding 15
     - Performance bias (blinding of participants and personnel) 15
     - Detection bias (blinding of outcome assessment) 15
   - 4.6.3 Incomplete outcome data 15
   - 4.6.4 Selective reporting 16
   - 4.6.5 Other potential sources of bias 16
   - 4.7 Effects of interventions: 17
   - 4.7.1 Successful discontinuation rate 17

4.7.2 withdrawal symptoms.....18
4.7.3 Adverse events.....18
4.7.4 Quality of life.....19
4.7.5 Depressive symptoms.....19
4.7.6 Anxiety symptoms.....20
5. Discussion 21
5.1 Summary of main results 21
5.2 Discontinuation versus continuation of long term antidepressants 21
5.3 Potential biases in the review process 22
5.4 Agreements and disagreements with other studies or reviews 22
6. Conclusions 23
7. References 24
8. Appendices.....31
8.1 Abbreviations 31
9.Characteristic of Studies.....32
10.Personal reflections.....106

2. Introduction:

Antidepressants are a class of medications that may have influence on transmission of neurotransmitters in the brain, such as serotonin, norepinephrine, and dopamine which play a role in regulating mood, emotions, and anxiety levels (1), (2).By affecting neurotransmitter activity, antidepressants can help alleviate symptoms of depression and reduce anxiety in individuals with anxiety disorders including generalized anxiety disorder (GAD), panic disorder, social anxiety disorder, specific phobias, and others (3).

The major classes of antidepressants are: (4)

1. Selective serotonin reuptake inhibitors (SSRIs): citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline.
2. Serotonin-noradrenaline reuptake inhibitors (SNRIs): duloxetine, venlafaxine, desvenlafaxine, milanacipran, levomilnacipran.
3. Noradrenaline reuptake inhibitors (NARIs): reboxetine.
4. Tricyclic antidepressants (TCAs) and related: amitriptyline, clomipramine, dosulepin, , imipramine, nortriptyline, maprotiline.
5. Noradrenaline-dopamine reuptake inhibitors (NDRIs): bupropion.
6. Monoamine oxidase inhibitors (MAOIs): phenelzine, moclobemide, tranylcypromine

Other drugs are also used to treat depression:

1. Melatonergic antidepressants: agomelatine.
2. Noradrenergic and specific serotonergic antidepressant (NaSSA) and related: mirtazapine, mianserin.
3. Serotonin antagonist and reuptake inhibitors (SARIs): trazodone.
4. Multi-modal serotonin reuptake inhibitor and receptor blocker: vortioxetine, vilazodone.
5. Hypericum perforatum (St John's Wort).

The prevalence of anxiety and depressive disorders has been observed to increase during covid-19 period. The data was established through self-reporting in National Health survey. It suggests that a larger proportion of the population experienced anxiety problems (between 15% and 24%) during the pandemic, compared to the 11% reported in 2018. Similarly, the prevalence of depressive disorders was higher during the pandemic (between 13% and 22%) compared to the 9.5% recorded in 2018. In March 2022, 11% of respondents suffered from both anxiety and depressive disorders, 8% from an anxiety disorder (without depression) and 5% from a depressive disorder (without anxiety). In total, 24% of the Belgian population presented with anxiety or a depressive disorder. (5)

The prevalence of anxiety and depressive disorders are higher in the Walloon Region compared to the Brussels Capital Region and the Flemish Region whereas the Brussels Capital Region has a higher prevalence compared to the Flemish Region (5). The consumption of antidepressants has also soared substantially and continues to rise. The highest use per population in the Convention on the Organisation for Economic Co-operation and Development (OECD) Health Report is reported in Iceland, Australia, Portugal, UK, Sweden, Canada, and Belgium (6). According to data of 2020 about 72.4 % of Belgians take antidepressants for a duration of more than 12 months. (7)

The treatment recommendations for mild depression suggest avoiding the routine prescription of antidepressants. Mild depression may resolve with exercise or watchful waiting, but psychotherapy or antidepressants could be used if initial efforts fail. First-line treatment recommendations for moderate major depressive disorder include antidepressant monotherapy, psychotherapy, and the

combination of both. Severe depression may require the combination of an antidepressant and psychotherapy. (8), (9).
Antidepressant drugs are absolutely indicated for patients with major depression (characterized by marked symptoms and functional impairment). Belgian guidelines recommend making a selection between a selective serotonin reuptake inhibitor (SSRI) or a tricyclic antidepressant (TCA) as a drug of choice in primary care. (8), (10) Dutch guideline for primary care does not recommend TCA as a drug of first choice anymore however, there is no need to switch previously started TCA to SSRI in case of satisfactory results and TCA can be considered again as a drug of choice if patient has previously used it. (9). It may be useful to associate a benzodiazepine for a short period of time in these cases of depression with anxiety or agitation. (10).
The selection of antidepressant determined by its efficacy and tolerability, the depressive presentation, preference of patient and drug interactions. In the primary care selection between SSRI or a TCA can also base on the desired avoidance of side effects and the presence of comorbidity and/or concomitant medication. Risk of suicide should also be taken in consideration. Shared decision making with the patient remains critical if an antidepressant is prescribed. When starting an antidepressant, the patient must be thoroughly informed about the expected desired and undesirable effects. Additionally, regular follow-up (every one to two weeks) should be planned, especially during the first month. In patients younger than 30 years of age, increased attention to a possible increase in suicidal ideation is desirable when starting an antidepressant. (Partial) response to the started antidepressant is expected within 4 to 6 weeks. (8)
Within the group of SSRIs, there is no real preferred product, and the starting dose is the same as the maintenance dose. The most common side effects of SSRI antidepressants may include drowsiness, weight gain, insomnia, sexual dysfunction, anxiety, dizziness, headache, blurred vision, nausea, and rash. SSRIs are also linked with increased bleeding due to changes in platelet function. It is necessary to approach this with caution if they are taken with anticoagulants or non-steroidal anti-inflammatory drugs (NSAIDs). There is an increased risk of serotonin toxicity when taking SSRIs in combination, with St John's herb, monoamine oxidase inhibitors and other drugs with (MAOIs). (8), (10), (11)
For tricyclic antidepressants, the dose is gradually increased to the maintenance dose, among TCAs, amitriptyline is a sedating product with strong anticholinergic effects. Nortriptyline is a more activating product with fewer anticholinergic effects. (10)
The relapse/recurrence of depressive symptoms after successful treatment is common and is major clinical concern. The risk of relapse/recurrence can be reduced by continuation of antidepressant after acute treatment. Guidelines recommend continuing antidepressant therapy for at least 6 months after successful acute phase treatment to prevent relapse/recurrence and up to 1 years in case of recurrent depression. (10), (9), (10.) It can also be decided not to stop antidepressants in certain situations, for example, previous, severe persistent depression. (9)
Guidelines also advise gradual discontinuation of antidepressant drugs after successful treatment; abrupt termination of antidepressants may lead to temporary withdrawal symptoms. (10), (8), (9). The risk of discontinuation symptoms is higher if a higher dose was required during treatment or withdrawal symptoms occurred with a missed dose and previous quit attempts have been failed. (9).

- **Why it is important to do the review:**

Due to having scarce evidence for the optimal duration of continuation and maintenance treatment, most guidelines are based on expert opinion and consensus. Previous reviews compared approaches to discontinuation with continuation of antidepressants for six months but could not provide any conclusion. The aim of this new review (with meta-analysis) is to assess the effectiveness and safety of discontinuation versus continuation of long-term antidepressant use for depressive and anxiety disorders in adults who have been taking them for a period ranging from 3-6 months.

- **PICO=**

Patient or population: participants with depressive or anxiety disorders with 3–6-month treatment, after improvement.

Setting: Primary care and specialist mental healthcare services.
Intervention: Discontinuation of AD (placebo).
Comparison: Continuation.

Outcome: Successful discontinuation rate, adverse events, withdrawal symptoms.

3. Method:

3.1 Search method:

We performed a meta-analysis of studies that were excluded from previous Cochrane review on discontinuation of antidepressant treatment after six months of treatment or longer (4). We included (RCTs) comparing the effects of discontinuation with the continuation of antidepressants. The participants included individuals who had been prescribed antidepressants for a duration of 12 to 24 weeks. Our study focused on examining the benefits (e.g., successful discontinuation rate), and potential harms associated with discontinuation interventions such as return of the depressive or anxiety symptoms, side effects, and withdrawal symptoms for individuals taking antidepressants. Our primary outcomes were successful discontinuation rate, adverse events, withdrawal symptoms. Secondary outcomes included: depressive symptoms, anxiety symptoms, quality of life.

3.2 Selection of Studies:

Three review authors autonomously screened the full text, and selected studies for inclusion and exclusion according to criteria mentioned in methodology. We resolved disagreement through discussion or, if required, we consulted co-promoter EVL. All selection process has been documented in detail to complete Characteristics of included studies, and characteristics of excluded studies tables.

3.3 Data extraction and management:

Characteristics and outcome data from included studies was independently extracted by all 3 review authors. We extracted the following characteristics.
Methods: study design, total duration of study, details of any 'run-in' period, number of study centers and location, study setting.
Participants: number, mean age, age range, gender, severity of condition, duration of antidepressant treatment before trial, comorbidity.
Setting: primary care versus outpatient psychiatric hospital versus nursing home, Diagnostic criteria, inclusion criteria, and exclusion criteria.
Interventions: intervention inclusive mode of discontinuation (gradually or abruptly).
Outcomes: primary and secondary outcomes specified and collected.
Funding and notable conflicts of interest of trial authors.
We noted in the 'Characteristics of included studies' table if trials did not report outcome data in a usable way, then disagreements were resolved by consensus. Data was transferred into the Review Manager 5 file (Review Manager 2014) and was double-checked for errors.

3.4 Main planned comparisons:

Discontinuation of antidepressant versus continued antidepressant use.

3.5 Assessment of risk of bias in included studies:

The risk of bias for each study was recorded independently by three review authors. We used the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2017) to assess risk of bias. Disagreements were resolved by discussion. We recorded the risk of bias regarding the following domains.

Random sequence generation, Allocation concealment, blinding of participants and personnel, Blinding of outcome assessment. Incomplete outcome data Selective outcome reporting, other bias. We recorded our 'Risk of bias's assessment in the 'Risk of bias's table.

3.6 Measures of treatment effect:

Dichotomous data:

Dichotomous data was analyzed as proportions and the pooled estimates as odds ratios (OR) with 95% confidence intervals (95% CI).

Continuous data:

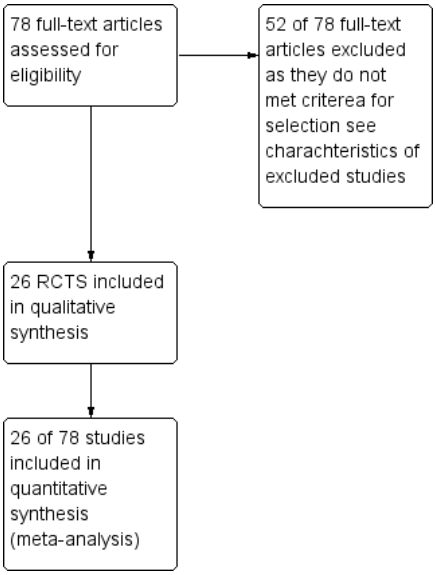
Three review authors independently entered data from various scales. We recorded continuous data as means and expressed the pooled estimate as mean difference (MD), if the studies used the same scale, or standardized mean difference (SMD) if they used different scales to measure the same outcome, with a standard deviation (SD). We calculated a 95% CI for each estimate and recorded the reported HR or calculated the estimated HR from the information presented in the studies.

3.7 Unit of analysis issues:

Participants in RCTs are the unit of analysis.

4. Results:

Out of 78 studies we included **26** studies in our review and excluded **52** studies. The reasons for excluding **52** records are listed under Characteristics of excluded studies.



4.1.1 Included studies:

We included 26 studies with **8083** participants (see Characteristics of included studies).

We included only the study arms with participants with unipolar depression or anxiety disorders (e.g., generalised anxiety disorder, panic disorders) who were treated with antidepressants (or discontinued the antidepressant).
7 studies included multiple different treatment arms after randomization: 3 treatment arms in (Robinson 1991; Zajecka 1998; Dinan 2001; Fava 2002) and 4 treatment arms in (Wetherell 2013; Reimherr 1998; Stewart 1998).
One study included two different treatment arms before randomization; each treatment arm was randomized separately, but results were reported in a single publication (Georgotas 1989).

4.1.2 Design:

All 26 studies were RCTs with a placebo arm; All 26 studies compared discontinuation with continuation of antidepressants and discontinuation of antidepressant occurred during "continuation" treatment or “maintenance" treatment (as described by study authors in introduction) after stabilization (treatment duration with antidepressants is 12-24 weeks before randomization to achieve stabilization/remission).
(Zajecka 1998, Wetherell 2013, Walker 2000, Stein 2012, Rosenthal 2013, Reimherr 1998, Thase 2001, Ferguson 2007, Gorwood 2007, Harrison 1986, Lustman 2006, Lyketsos 2011, McGrath 2006, Montgomery 2005, Stewart 1998, Dinan 2001, Davidson 2008, Boulenger 2012, Baldwin 2012, Allgulander 2006, Robinson 1991, Georgotas 1989, Hochstrasser 2001, Alexopolous 2000, Fava 2002, Durgam 2019)
8 studies included multiple treatment phases before randomization to antidepressants or to placebo ("multi-phase studies"). Participants meeting response criteria at the end of the treatment phase were allowed to enter the subsequent phase:
Four studies used a two-phase method (Ferguson 2007, Hochstrasser 2001, McGrath 2006, Alexopolous 2000).
Four studies employed a three-phase method (Georgotas 1989, Wetherell 2013, Rosenthal 2013, Robinson 1991).
1 study (Fava 2002) included multiple treatment phases post randomization.
1 study (Durgam 2019) included multiple treatment phases pre and post randomization.

4.1.3 Aims of studies:

The objective of this review was to evaluate the effectiveness and safety of approaches for discontinuation versus continuation of antidepressant use (for a period of 12-24 weeks). All studies investigated discontinuation versus continuation of antidepressants, but they described initially different study aims. "Relapse prevention" discontinuation studies 25 studies, the initial aim of these studies was to examine how continuation of long-term antidepressant could prevent relapse.
In the current study, antidepressants were given to selected participants for 12-24 weeks which later were divided into two groups: responders whose symptoms improved and non-responders. The participants unable to tolerate the antidepressant, non-adherent participants, and participants did not show their consent to proceed further for some reason were excluded from the trial. Responders subjected to randomization to remain on antidepressants or to terminate the antidepressant by changing the antidepressant with a placebo. (Wetherell 2013, Walker 2000, Thase 2001, Stein 2012, Rosenthal 2013, Robinson 1991, Reimherr 1998, Allugander 2006, Baldwin 2012, Boulenger 2012, Davidson 2008, Dinan 2001, Durgam 2019, Stewart 1998, Fava 2002, Ferguson 2007, Hochstrasser 2001, McGrath 2006, Georgotas 1989, Lustman 2006, Gorwood 2007, Lyketsos 2011, Montgomery 2005, Harrison 1986, Alexopolus 2000, Wetherell 2013)investigated the effectiveness of an intervention designed to facilitate discontinuation of long-term antidepressants: with cognitive behavior therapy.

4.1.4 Setting:

All 26 studies included participants who were living in the community and were conducted in a psychiatric outpatient setting and/or general practice/primary care settings.
Two studies were conducted in general practice/primary care settings (Stein 2012, Wetherell 2013)
12 studies were conducted in the USA (Thase 2001, Robinson 1991, Reimher 1998, Wetherell 2013, Alexopolus2000, Durgam 2019, Georgotas 1989, Harrison 1986, Lustman 2006, McGrath 2006, Stewart 1998, Davidson 2008)
The most studies were from many countries worldwide:
Canada (Walker 2000, Stein 2012, Boulenger 2012)
Denmark, Estonia, Hungary (Stein 2012)
Sweden (Stein 2012, Boulenger 2012)
United Kingdom (Hochstrasser 2001, Boulenger 2012)
Finland (Stein 2012, Boulenger 2012, Baldwin 2012)
Austria (Davidson 2008, Boulenger 2012)
France (Baldwin 2012, Davidson 2008, Boulenger 2012)
Germany (Davidson 2008, Boulenger 2012)
Portugal, Netherlands (Davidson 2008)
Australia, Belgium, India, the Republic of Korea, Norway, Poland, Taiwan, Thailand, Turkey (Boulenger 2012)
South Africa (Rosenthal 2013, Boulenger 2012, Baldwin 2012)
Argentina, Chile, Colombia, Costa Rica, Estonia, Hungary, Russian Federation (Baldwin 2012)
The setting was not described in 4 studies (Zajecka 1998, Dinan 2001, Fava 2002, McGrath 2006).

4.1.5 Sample size:

Sample size varied from 12 in the study of (Harrison 1986) to 874 participants in (Rosenthal 2013). The average sample size was 443. Most studies included adults between 18 and 65 years of age. 5-studies included only participants 65 years of age and older (Wetherell 2013, Gorwood 2007, Alexopolus2000, Lyketsos 2011). 19 studies included more female than male participants.

4.1.6 Indication for antidepressant:

Depression

15 studies included participants with the main diagnosis of unipolar major depressive disorder (Thase 2001, Rosenthal 2013, Robinson 1991, Reimherr 1998 , Zajecka 1998, Boulenger 2012, Stewart 1998, Durgam 2019, Alexopolous 2000, Zajecka 1998, Georgotas 1989, Lustman 2006, McGrath 2006, Gorwood 2007, Lyketsos 2001). 1 study included participants with Dysthemic disorder with long histories of depression disorder (mean duration = 15 years) (Harrison 1986). 1 study included participants with recurrent depression (Hoschstrasser 2001)

Anxiety

9 studies included participants with anxiety disorder: 1 included participant with social phobia (Walker 2000), and 6 included participants with generalized anxiety disorder (Stein 2012, Wetherell 2013, Allugander 2006, Baldwin 2012,Dinan 2001, Davidson 2008, Montgomery 2005) and 1 study with panic disorders (Ferguson 2007)

Depression and anxiety

2 studies (Dinan 2001, fava 2002) included participants with anxiety disorder and generalized depression. (Number of participants with anxiety and generalized depression are not separately described)

Suicide, suicide attempt, or suicidal ideation

Most studies excluded participants at high risk for suicide. Six studies reported suicide, suicide attempt, or suicidal ideation as a criterion of relapse or as a (serious) adverse event (Rosenthal 2013, Thase 2001, Hochstrasser 2001, Durgam 2019, Boulenger 2012, Davidson 2008)

4.1.7 Duration:

All studies had to meet the main inclusion criteria that participants received antidepressants for a period of 12-24 weeks for depressive or anxiety disorder to achieve remission during pre-randomization phase. Prerandomized phase was in 9 studies about 12 weeks (Gorwood 2007, Lyketsos 2011, Montgomery 2005, Stewart 1998, Boulenger 2012, Allgulander 2006, Zajecka 1998, Wetherell 2013, Reimherr 1998). 4 studies included participants receiving maintenance treatment (Robinson 1991, Rosenthal 2013, Georgotas 1989, Hochstrasser 2001). During Post randomized phase duration of treatment with antidepressants varied from 6 weeks to 2 years among different studies.

4.1.8 Type:

Trials examined effects of discontinuation of several antidepressants including:
Fluoxetine (Reimherr 1998, Zajecka 1998, Dinan 2001, Stewart 1998, Fava 2002, McGrath 2006). Sertraline (Walker 2000, Lustman 2006). Escitalopram (Wetherell 2013, Allugander 2006, Gorwood 2007, Lyketsos 2011, Montgomery 2005). Mirtazapine (Thase 2001). Citalopram (Hochstrasser 2001). Agomelatine (Stein 2012) Phenelezine (Robinson 1991, Harrison 1986). Desvenlafaxin (Rosenthal 2013). Nortriptyline (Alexopoulous 2000). Vortioxetine (Baldwin 2012, Boulenger 2012). Duloxetine (Davidson 2008). Levomilnacipran ER (Durgam2019). Venlafaxine ER (Ferguson 2007). Nortriptyline and Phenelezine were used in one study (Georgotas 1989). The dose of antidepressant given at the start of the trial varied within and between studies.

4.1.9 Severity of depressive disorder/anxiety disorder at the time of randomization:

All studies needed participants to be in remission to enter the discontinuation trial and narrated remission criteria. The definition of response/remission varied widely between studies and involved specific scores on scales, clinical judgement, guidelines, or a mix of criteria (See characteristics of studies for details).

4.2 Outcome measures :

4.2.1. Discontinuation Rate:

22 studies (1827 participants) compared abrupt discontinuation to continuation of long-term antidepressants.
Only 4 studies (1256 participants) compared discontinuation by "tapering" (one week or longer) to continuation of long-term antidepressants (Allgulander 2006, Ferguson 2007, Davidson 2008, Rosenthal 2013). Most tapering regimens lasted 2 weeks or less. Antidepressants with their tapering schemes are following:
Allgulander 2006: tapering of escitalopram over one week before starting placebo.
Ferguson 2007, Davidson 2008: patients who were randomly assigned to placebo underwent a 2-week taper of study medication. Venlafaxine and Duloxetine respectively.
Rosenthal 2013: patients who were randomly assigned to receive placebo were tapered to double-blind treatment with desvenlafaxine 25 mg/d during the first week of the double-blind period.
one study included a psychological co-intervention cognitive-behavioral therapy (CBT) in prerandomisation phase (Wetherell 2013).
None of studies reported discontinuation rate as a primary outcome.

4.2.2. Withdrawal symptoms:

One study reported withdrawal symptoms Hochstrasser 2001 potential discontinuation symptoms: dizziness, headache, nausea, and vertigo in the first few weeks following randomization. Possible discontinuation symptoms were evaluated by assessing, for each patient and adverse event, whether the event was present at randomization (day-I of prophylactic treatment) and whether, within days

2-14, the event appeared, stopped, or changed intensity with respect to status at day-1. The median duration of an episode was 21 days for dizziness, 19 days for headache, 11 days for vertigo and 10 days for nausea.

4.2.3. Adverse events:

Adverse events were measured in 10 studies and therefor these studies were considered suitable for pooling (Thase 2001, Stein2012, Rosenthal 2013, Allgulander 2006, Boulenger 2012, Durgam 2019, Gorwood 2007, Montgomery 2005, Ferguson 2007, Baldwin 2012).

Serious adverse were reported in five studies (Allgulander 2006, Boulenger 2012, Durgam 2019, Baldwin 2012, Hochstrasser 2001)

Allgluander 2006 (n=166) The tolerability and safety evaluations were based on spontaneously reported adverse events (AEs), vital signs, body weight, physical examinations, and clinical safety laboratory tests.

Boulenger 2012 (n=249) Adverse events and serious adverse events were recorded by asking a non-leading question (such as, 'How do you feel?') at each visit, starting at baseline. All AEs (including any change in concurrent illnesses or new illnesses) either observed by the investigator or reported spontaneously by the patient were recorded.

Durgam 2019 (n=166) AEs, serious AEs (SAEs), and vital signs were recorded at all study visits. Clinical laboratory tests and electrocardiograms were performed during screening, at randomization, and at the end of double-blind treatment.

Adverse events are recorded by number of participants with newly emergent AE. Newly emergent AE was an AE that was not present before the first dose of double-blind treatment or that increased in severity during the double-blind phase.

Baldwin 2012 (n=250) AE were recorded by asking patients a nonleading question (such as, 'How do you feel'?) at each visit, starting at the baseline. All AEs (including any change in concurrent illnesses or new illnesses) that were either observed by the investigator or reported spontaneously by the patient were recorded.

Thaes 2001 (n=410) AE were recorded by the treating g psychiatrist according to standard conventions. The query "Have you experienced any adverse events or side effects since your last visit?" was used to elicit the patient's spontaneous reports. Both new-onset adverse events and those that persisted from visit to visit were recorded. No serious adverse were reported.

Rosenthal 2013 (n=548) Monitoring of adverse events (AEs; categorized based on Medical Dictionary for Regulatory Activities [MedDRA]33 terminology), concomitant medications, and administration of the Columbia-Suicide Severity Rating Scale (C-SSRS).

Stein 2012 (n=227) Emerging adverse events (AEs) spontaneously reported by the patient or elicited by the investigator and were not dependent on using a specific instrument (eg, the UKU Side Effects Rating Scale). No serious adverse were reported.

Gorwood 2007 (n= 405) The tolerability and safety evaluations were based on spontaneously reported adverse events (AEs), vital signs, body weight, and physical examination. No serious adverse were reported.

Montgomery 2005 (n=517) Safety and tolerability were evaluated based on spontaneously reported adverse events, electrocardiograms (ECGs), vital signs (systolic and diastolic blood pressure and pulse rate), weight, physical examinations, and clinical safety laboratory tests (hematology and biochemistry).The 43-item Discontinuation Emergent Signs and Symptoms (DESS) checklist was used (after the general open questioning used for the recording of adverse events) at the end of the open-label period (at randomization) and 1 and 2 weeks after randomization. No serious adverse were reported.

Harrison 1986 (n=12) Was considered unsuitable for pooling; it did not report the number of (serious) adverse events in general but reported that the adverse event profile in the citalopram group was comparable to that of the placebo group.

Ferguson 2007: (n=313) reported adverse events as commonly reported treatment emergent adverse events but it did not report how these Safety assessments were evaluated.

4.2.4. Depressive symptoms: (as defined by study authors)

19 studies contributed data for this outcome.

Thirteen studies measured depressive symptoms with HAMD scale (MccGrath2006, Thase 2001, Rosenthal 2013, Robinson 1991, Reimherr 1998, Gorwood 2007, Georgotas 1989, Harrison 1986, Lyketsos 2011, Lustman 2006, Boulenger 2012, Dinan 2001, Stewart 1998)

Seven studies used Montgomery Åsberg Depression Rating Scale MADRS Scale for measurement of depressive symptoms (Baldwin2012, Allgulander 2006, Boulenger 2012, Durgam2019, Gorwood 2007, Hochstrasser 2001, Lyketsos 2011).

4.2.5. Anxiety symptoms:

9 studies contributed data for this outcome. (Baldwin2012, Allgulander 2006, Boulenger 2012, Davidson2008, Dinan2001, Walker 2000, Montgomery 2005, Stein2012, Dinan 2001)
Walker 2000 used different outcome scales. The primary efficacy assessments were the percentage of patients regarded enhanced a lot on the Clinical Global Impression (CGI) improvement item and the mean changes from baseline to study endpoint in total score on the social phobia subscale of the Marks Fear Questionnaire and total score on the Brief Social Phobia Scale and (Hamilton Anxiety Rating Scale [HARS].
Stein2012 investigated anxiety symptoms by using (Hamilton Anxiety Rating Scale [HARS].
Dinan 2001, Efficacy of Antidepressiva vs placebo on Anxiety symptoms are shown in fig 2 with HAMD anxiety score.

4.2.6. Quality of life:

Six studies assessed quality of life with SDS for 3 life domains: work/school, social life, and family/home responsibilities (Davidson2008, Allgulander 2006, Durgam 2019, Walker 2000, Montgomery 2005, Baldwin 2012).
However, Montgomery 2005 measured only social life, family life with SDS scale. SDS work domain was not reported in this study.

4.3 Funding:

11 studies were supported by a grant from the pharmaceutical industry (Walker 2000, Thase 2001, Stein 2012, Rosenthal 2013, Boulenger 2012, Davidson 2008, Durgam 2019, Stewart 1998, Fava 2002, Lustman 2006, Lyketsos 2011). 8 studies also reported non-commercial sponsorship (Robinson 1991, Reimherr 1998, Ferguson 2007, Gorwood 2007, Georgotas 1989, Hochstrasser 2001, McGrath 2006, Montgomery 2005)**.** The source of funding was not described in 7 studies (Zajecka 1998, Wetherell 2013, Alexopoulos 2000, Allgulander 2006, Baldwin 2012, Dinan 2001, Harisson 1986)

4.4 Exclusion criteria :

Most studies excluded participants at high risk for suicide, drug abuse, anxiety disorders, and other Axis I or Axis II disorders (see characteristics of included studies).

4.5 Excluded studies:

We excluded 50 studies from the review (see characteristics of excluded studies). The most common reason for exclusion was that participants had received antidepressant treatment for less than 12 weeks or more than 6 months (e.g., Goodwin 2009, Goodwin 2013, Kamijima 2005, Kamijima 2006, Liebowitz 1999, Michelson 1999, Montgomery 1993, Baldwin 2006, Cohen 2006, Doogan 1992, Curtis 1993, Reynolds 1999, Rosenbaum 1998, Stein 1996, Stocchi 2003).

Other studies did not report total treatment duration before randomisation (e.g., Glen 1984, OADIG 1993, CroM 2002, Dobson 2008)

4.6 Risk of bias in included studies:

We assessed each of the 26 included studies for risk of bias across the six domains, using the Cochrane 'Risk of bias' assessment tool Higgins 2017 (12), as described in the Methods (Assessment of risk of bias in included studies). We have reported these assessments in the 'Risk of bias' table associated with each study.

4.6.1 Allocation:

Sequence generation:

We judged 16 studies to be at low risk of bias for this domain. All clearly described the method of sequence generation used **(**Allugander 2006, Boulenger 2012, Davidson 2008, Durgam 2019, Alexopoulos 2000, Baldwin 2012, Stewart 1998, Rosenthal 2013, Stein 2012, Ferguson 2007, Gorwood 2007, Hochstrasser 2001, Lustman 2006, Lyketsos 2011, McGrath 2006, Montgomery 2005).

We judged 10 studies as having unclear risk as they did not mention or provided insufficient information on the method of sequence generation used (Fava 2002, Dinan 2001, Reimherr 1998, Robinson 1991, Zajecka 1998, Thase 2001, Walker 2000, Georgotas 1989, Harrison 1986, Wetherell 2013).

Allocation concealment:

Allocation concealment was described in sufficient detail to assess risk of bias as low in 16 studies (Alexopoulos 2000, Allgulander 2006, Baldwin 2012, Boulenger 2012, Davidson 2008, Durgam 2019, Fava 2002, Thase 2001, Stein 2012, Ferguson 2007, Gorwood2007, Harrison 1986, Lustman 2006, Lyketsos 2011, McGrath 2006, Montgomery 2005).

Risk of allocation concealment bias was unclear in 10 studies as the method of concealment is not described or is not described in sufficient detail to allow a definitive judgement (Stewart 1998, Dinan 2001, Wetherell 2013, Walker 2000, Zajecka 1998, Robinson 1991, Rosenthal 2013, Reimherr 1998, Georgotas 1989, Hochstrasser 2001).

4.6.2 Blinding:

Performance bias: (blinding of participants and personnel)

It was determined that 16 studies having low risk of performance bias. These studies explicitly described the technique used in blinding (Alexopoulos 2000, Allgulander 2006, Baldwin 2012, Boulenger 2012, Davidson 2008, Durgam 2019, Fava 2002, Zajecka 1998, Thase 2001, Robinson 1991, Rosenthal 2013, Stein 2012, Gorwood2007, Lustman 2006, Lyketsos 2011, McGrath 2006). 9 studies were classified to have unclear risk of bias; these studies did not specify whether participants and personnel were blinded or how they were blinded. (Stewart 1998, Dinan 2001, Wetherell 2013, Walker 2000, Reimherr 1998, Georgotas 1989, Harrison 1986, Hochstrasser 2001, Montgomery 2005). We assessed one study as having high risk of bias: due to knowledge of the allocated interventions by participants and personnel during the study (Ferguson 2007).

Detection bias: (blinding of outcome assessment)

It was noticed that 8 studies to be at low risk of detection bias as they provided a clear description of the method of blinding of outcome (Baldwin 2012, Robinson 1991, Rosenthal 2013, Stein 2012, Zajecka 1998, Gorwood2007, Lustman 2006, Lyketsos 2011).

We evaluated 17 studies as being at unclear risk; study authors did not specify whether outcome assessors were blinded or how they were blinded (Alexopoulos 2000, Allgulander 2006, Boulenger 2012, Davidson 2008, Durgam 2019, Fava 2002, Stewart 1998, Dinan 2001, Thase 2001, Reimherr 1998, Walker 2000, Ferguson 2007, Georgotas 1989, Harrison 1986, Hochstrasser 2001, McGrath

2006, Montgomery 2005). We assessed one study as having high risk of bias; authors reported possible bias due to absence of a global outcome measure (Wetherell 2013).

4.6.3 Incomplete outcome data:

It was determined that 4 studies to be at low risk of attrition bias because there were no missing data, all study dropouts were reported, or the number of dropout participants was low (< 20%) and was similar across treatment groups (Wetherell 2013, Thase 2001, stein 2012, Harrison 1986).

We judged 10 studies to be at unclear risk as they did not report the reasons for dropout or the number of dropouts was not clear from the text (Alexopoulos 2000, Allgulander 2006, Boulenger 2012, Durgam 2019, Fava 2002, Stewart 1998, Dinan 2001, Baldwin 2012, Reimherr 1998, Georgotas 1989). 12 studies were determined to be at high risk as a large proportion of data were missing and/or there was an imbalance in the number of missing participants across treatment groups (Davidson 2008, Walker 2000, Zajecka 1998, Robinson 1991, Rosenthal 2013, Ferguson 2007, Gorwood2007 , Hochstrasser 2001, Lustman 2006, Lyketsos 2011, McGrath 2006, Montgomery 2005).

4.6.4 Selective reporting:

22 studies (88%) did not succeed in containing withdrawal symptoms, which is the fundamental result in drug discontinuation trials. Therefore, we examined that without measuring withdrawal symptoms, a substantial source of bias will be introduced. Adverse events of antidepressants were measured by a total of 15 studies, but this result seems biased as it did not distinguish withdrawal symptoms from adverse events of antidepressants. None of the studies adjusted for withdrawal symptoms.

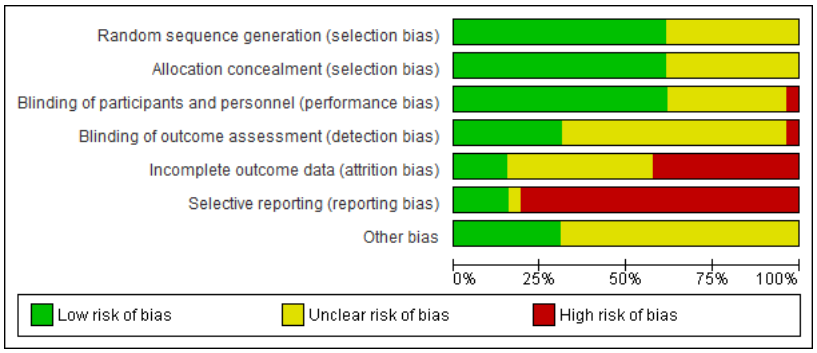
In the primary results, successful discontinuation rate and adverse events were not reported in 25 (92.5%), and 6 (23%) trials. The secondary outcomes depressive symptoms, quality of life, were not clearly reported in 21 (80%), trials. Data on suicide, suicide attempt, or suicidal ideation were not reported in 19 (76.3%) trials; Furthermore, numerous studies did not delineate all outcomes described in the methods section, or the data was reported incompletely.

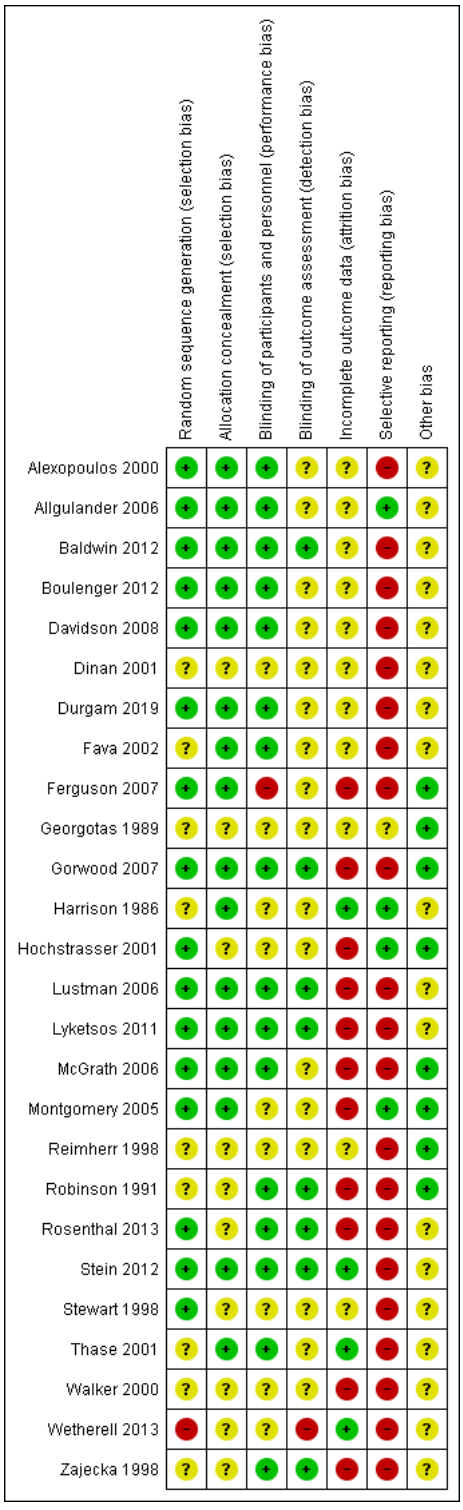
While following recommendations provided in the Cochrane Handbook for Systematic Reviews of Interventions, and in considering all relevant outcomes for a study-level judgement (Higgins 2017), we noticed 4 studies, out of rest all, at low risk of reporting bias(Allgulander 2006, Hochstrasser 2001, Harisson 1986, Montgomery 2005).

4.6.5 Other potential sources of bias:

We noticed, 18 studies receiving support from the pharmaceutical industry or reporting an unclear source of funding to be at unclear risk for industry sponsorship bias (Walker 2000, Thase 2001, Stein 2012, Rosenthal 2013, Boulenger 2012, Davidson 2008, Durgam 2019, Stewart 1998, Fava 2002, Lustman 2006, Lyketsos 2011, Zajecka 1998, Wetherell 2013, Alexopoulos 2000, Allgulander 2006, Baldwin 2012, Dinan 2001, Harisson 1986).

We judged 8 studies with only non-commercial sponsorship to be at low risk for industry sponsorship (Robinson 1991, Reimherr 1998, Ferguson 2007, Gorwood 2007, Georgotas 1989, Hochstrasser 2001, McGrath 2006, Montgomery 2005).





4.7 Effects of interventions:

Abrupt discontinuation versus continuation of long-term antidepressants is assessed in this meta-analysis. We focused on examining the benefits (e.g., successful discontinuation rate), and potential harms associated with discontinuation interventions such as return of the depressive or anxiety symptoms, side effects, and withdrawal symptoms for individuals taking antidepressants.

4.7.1 Successful discontinuation rate:

Out of twenty six included studies, none of the study reported successful discontinuation rate as an outcome.

4.7.2 withdrawal symptoms:

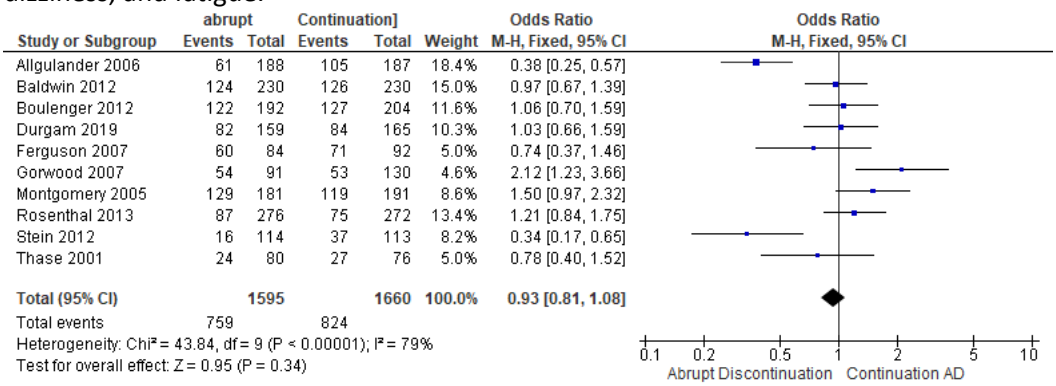
Only one study reported withdrawal symptoms (Hochstrasser 2001).
Possible withdrawal symptoms were evaluated by assessing, for each patient and adverse event, whether the event was present at randomization (day I of prophylactic treatment) and whether, within days 2-14, the event appeared, stopped, or changed intensity with respect to status at day 1.
Potential withdrawal symptoms: dizziness, headache, nausea, and vertigo in the first few weeks following randomization.
The median duration of an episode was 21 days for dizziness, 19 days for headache, 11 days for vertigo and 10 days for nausea.
Study authors reported a higher score for withdrawal symptoms at the end of the study in the discontinuation group compared to the continuation group (OR 7.23, 95% CI 3.24 to 16.15, 264 participants, 1 study). Discontinuation of antidepressants at randomization in this study was abrupt.
We judged this study to be at low risk of bias in the selective outcome reporting.

4.7.3 Adverse events:

10 studies studies contributed data on adverse events were considered suitable for pooling (Thase 2001, Stein2012, Rosenthal 2013, Allgulander 2006, Boulenger 2012, Durgam 2019, Gorwood 2007, Montgomery 2005, Ferguson 2007, Baldwin 2012).
7 study reported the incidence of adverse events (Thaes 2001, Allgulander 2006, Boulenger 2012, Baldwin 2012, Ferguson 2007, Gorwood 2007, Montgomery 2005) Serious adverse were reported in five studies (Allgulander 2006, Boulenger 2012, Durgam 2019, Baldwin 2012, Hochstrasser 2001)
Another 4-studies reported incidence -of treatment emergent adverse events (Rosenthal 2013, Stein 2012, Montgomery 2005, Ferguson 2007). In one study Durgam 2019 adverse events are recorded by number of participants with newly emergent AE.
The discontinuation group was comprised of 1595 participants whereas 1660 participants were included in the continuation group. In the pooled discontinuation group, 635 adverse events were reported (including withdrawal symptoms) compared to 698 in the continuation group, but there were no differences in adverse events between discontinuation and continuation of antidepressants (odds ratio (OR) 0.93 (CI 0.83- 1.08), 3255 participants, 10 studies). With the help of Cochrane 'Risk of bias' assessment tool for assessment risk of bias in included studies. We observed that all studies to be at high risk of bias in the domain of reporting bias.

- **Type of adverse events:**

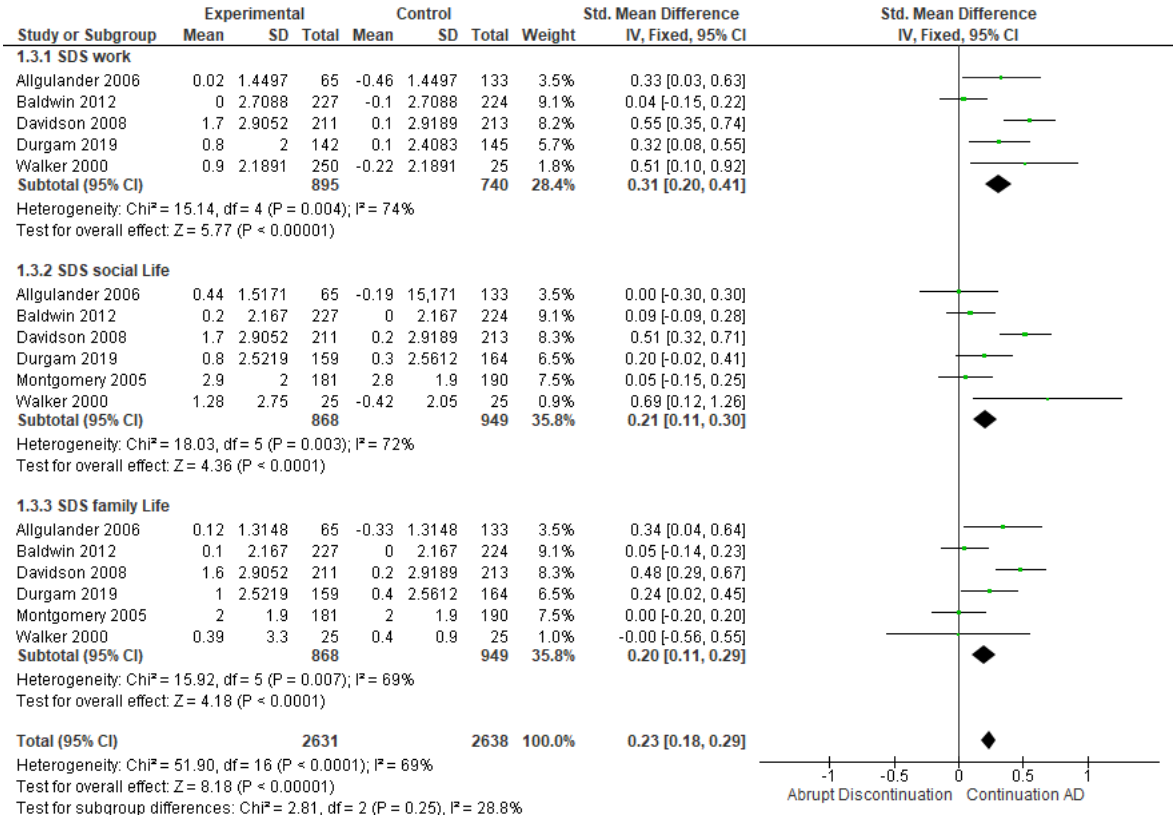
The adverse events experienced by antidepressant discontinuers were predominantly headache, insomnia, nausea, dizziness, malaise, flu-like symptoms, upper airway infection, anxiety, depression, decreased libido.
On the other hand, the most common adverse events reported by participants who continued taking their antidepressants included headache, flu-like symptoms, nausea, somnolence, insomnia, upper airway infection, anxiety, decreased libido, nausea, abdominal pain, weight loss, psychiatric disorder, dizziness, and fatigue.



For our secondary outcomes we included: depressive symptoms, Anxiety symptoms, Quality of life.

4.7.4 Quality of life:

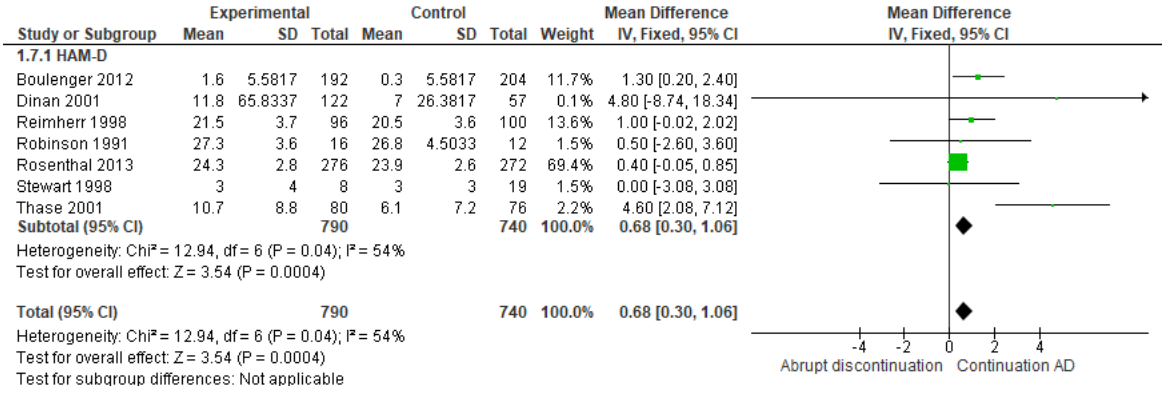
6 studies assessed quality of life with SDS for 3 life domains: work/school, social life, and family/home responsibilities (Davidson2008, Allgulander 2006, Durgam 2019, Walker 2000, Montgomery 2005, Baldwin 2012). However, Montgomery 2005 measured only social life, family life with SDS scale. SDS work domain was not reported in this study.
In the pooled continuation group, participants reported better quality of life in three domains: work/school, social life, and family/home responsibilities as compared to discontinuation group (MD 0.50, 95% CI 0.37 to 0.62 ,5269 participants, 6 studies)



4.7.5 Depressive symptoms:

19 studies contributed data on depressive symptoms, but they used different outcome scales. Thirteen studies measured depressive symptoms with HAMD scale (McGrath2006, Thase 2001, Rosenthal 2013, Robinson 1991, Reimherr 1998, Gorwood 2007, Georgotas 1989, Harrison 1986, Lyketsos 2011, Lustman 2006, Boulenger 2012, Dinan 2001, Stewart 1998)
Seven studies used Montgomery Åsberg Depression Rating Scale MADRS Scale for measurement of depressive symptoms (Baldwin2012, Allgulander 2006, Boulenger 2012, Durgam2019, Gorwood 2007, Hochstrasser 2001, Lyketsos 2011).
Pooled studies
7 studies used HAM-D to assess depressive symptoms and were considered suitable to pool (Thase 2001, Rosenthal 2013, Robinson 1991, Reimherr 1998, Boulenger 2012, Dinan 2001, Stewart 1998)
There were 790 participants in the pooled placebo group and 740 participants in the pooled antidepressant group.

790 participants were included in the pooled discontinuation group and 740 in the pooled continuation group. In the pooled discontinuation group, participants reported significantly higher scores on the HAM-D scale compared to those in the antidepressant group (MD 0.68, 95% CI 0.30 to 1.06; 1530 participants, 7 studies)



4.7.6 Anxiety symptoms:

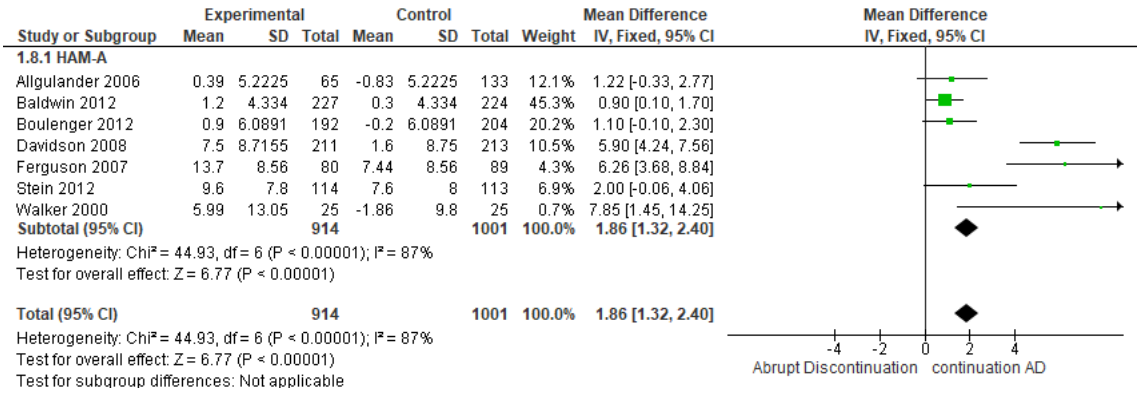
9 studies contributed data for this outcome (Baldwin2012, Allgulander 2006, Boulenger 2012, Davidson2008, Dinan2001, Walker 2000, Montgomery 2005, Stein2012, Dinan 2001). 7 studies were considered suitable to pool .

Walker 2000 used different outcome scales. The primary efficacy assessments were the percentage of patients rated much or very much improved on the Clinical Global Impression (CGI) improvement item and the mean changes from baseline to study endpoint in total score on the social phobia subscale of the Marks Fear Questionnaire and total score on the Brief Social Phobia Scale and (Hamilton Anxiety Rating Scale [HARS])

Stein2012 investigated anxiety symptoms by using (Hamilton Anxiety Rating Scale [HARS].

Dinan 2001, reported efficacy of antidepressants vs placebo of Anxiety symptoms with HAMD anxiety score.

Participants in the pooled discontinuation group (n = 914) showed higher scores on the HAM-A scale compared to those in the pooled antidepressant group (n = 1001) (MD 1.86, 95% CI 1.32 to 2.40 ,1915 participants, 7 studies)



5 Discussion:

5.1 Summary of main results:

In this review we included 26 RCTs with 8083 participants who had been taking long-term antidepressants (12-24 weeks). All 26 studies were RCTs with a placebo arm; All 26 studies compared discontinuation with continuation of antidepressants and discontinuation of antidepressant occurred during "continuation" treatment or “maintenance" treatment.

22 studies (1827 participants) compared abrupt discontinuation to continuation of long-term antidepressants.

Only 4 studies (1256 participants) compared discontinuation by "tapering" (one week or longer) to continuation of long-term antidepressants Most tapering regimens lasted 2 weeks or less. One study included a psychological co-intervention cognitive-behavioral therapy (CBT) in prerandomisation phase.

All 26 studies included participants who were living in the community and were conducted in a psychiatric outpatient setting and/or general practice/primary care settings. The setting was not described in 4 studies. Two studies were conducted in general practice/primary care settings.

Out of twenty-six studies, fifteen studies included participants primarily diagnosed with unipolar major depressive disorder. One study included participants with Dysthymic disorder , one study included participants with recurrent depression, eight studies included participants with anxiety disorder and 2 studies included participants with both anxiety disorder and generalized depression.

Twenty -two studies included adults between 18 and 65 years of age. Four studies included only participants 65 years of age and older. 19 studies included more female than male participants. Pooling was not possible for one primary outcome (successful antidepressant discontinuation rate, all 26 studies did not report our primary outcome successful antidepressant discontinuation rate. Only one study reported withdrawal symptoms. The results and analysis for data of each outcome are described in figures (see figures with analysis forest plot).

5.2 Discontinuation versus continuation of long-term antidepressants:

In this metanalysis, we included 26 randomized controlled trials (RCTs) with 8083 participants to assess the effectiveness and safety of approaches for discontinuation versus continuation of long-term antidepressant use for depressive and anxiety disorders in adults who have been taking them for a period ranging from 12 weeks to 24 weeks. Our primary outcomes were successful discontinuation rate, adverse events, withdrawal symptoms. Secondary outcomes included: depressive symptoms, Anxiety symptoms, Quality of life.

Twenty-six studies reported discontinuation of antidepressant. But none of these studies reported a successful discontinuation rate as a primary outcome. Almost all studies were designed to measure how continuation of long-term antidepressants could avoid relapse and recurrence rather than discontinuation success. Only one study Hochstrasser 2001 reported withdrawal symptoms as outcome.

None of the other included studies made adjustments for withdrawal symptoms therefore it is unclear to which extent misclassified withdrawal symptoms could have contributed to relapse rates. Discontinuation and certainly abrupt discontinuation can increase withdrawal symptoms (OR 7.23, 95% CI 3.24 to 16.15 ,264 participants, 1 study), anxiety symptoms (MD 1.86, 95% CI 1.32 to 2.40 ,1915 participants, 7 studies), depressive symptoms (MD 0.68, 95% CI 0.30 to 1.06; 1530 participants, 7 studies) compared to continuation of antidepressants. Quality of life is better in continuation group than discontinuation group (MD 0.50, 95% CI 0.37 to 0.62 ,5269 participants, 6 studies). There is no significant difference in group with discontinuation for adverse events (odds ratio (OR) 0.93 (95% CI 0.83- 1.08), 3255 participants, 10 studies) compared to continuation of antidepressants.

Only 5 studies reported serious adverse events. Most studies excluded participants at high risk for suicide. Six studies reported suicide, suicide attempt, or suicidal ideation as a criterion of relapse or as a (serious) adverse event (Rosenthal 2013, Thase 2001, Hochstrasser 2001, Durgam 2019,

Boulenger 2012, Davidson 2008). But none of the studies are pooled for suicide, suicide attempt, or suicidal ideation making it impossible to drive a conclusion regarding relation of suicidality to discontinuation of antidepressants.

5.3 Potential biases in the review process:

The results of this study must be interpreted in the context of several limitations.
Our co-promotor provided a list of 78 studies that were excluded from a previous review that compared approaches of discontinuation with continuation of antidepressants six months or more after stabilization but during the search process, we identified two studies out of 78 that we could not find via search on databases. Perhaps this may be a source of potential bias.
For the rest of the 76 studies three review authors autonomously screened the full text, selected studies for inclusion and exclusion according to criteria mentioned in methodology. We resolved disagreement through discussion or, if required, we consulted co-promoter EVL. We have recorded all selection processes in detail to complete Characteristics of included studies, and characteristics of excluded studies tables, each step was evaluated by two authors to reduce the risk of bias.
Overall, all studies were judged to be at high risk of bias in at least one domain. The most common high-risk domain was reporting bias, followed by attrition bias. High risk of attrition bias and withdrawal symptoms may be misdiagnosed as adverse events.
It was very important to differentiate between adverse events and withdrawal symptoms. HAM-D was prioritized scale but was not sufficient to differentiate between them. It is necessary to note that adverse events may include withdrawal symptoms because the studies could not distinguish between them. Safety of antidepressants was not evaluated in most studies; risk of suicide was reported in only 6 studies.
Wide variation in definition of remission among different studies is another source of bias. Follow-up durations were different in these studies, and this can also be a source of bias. Participants in our review received antidepressants for 12-24 weeks. The post-randomization period of antidepressant treatment ranged from 6 weeks to 2 years among different studies.
Almost all studies had methodological limitations and were judged to be at unclear or high risk in a relapse domain. In 10 studies, information on random sequence generation or allocation concealment, or both, was insufficient. One study was assessed as having high risk of performance bias due to knowledge of the allocated interventions by participants and personnel during the study.
We assessed one study as having high risk of detection bias; authors reported possible bias due to absence of a global outcome measured 17 studies having unclear risk of detection bias. 12 studies were assessed as having high risk for attrition bias due to missing data, high dropout, or unbalanced dropouts. 22 studies were assessed as having high risk of bias due to selective reporting. Failure to measure withdrawal symptoms was evaluated as a considerable source of bias. We considered 20 studies to be at unclear risk and one study at high risk for sponsorship bias.

5.4 Agreements and disagreements with other studies or reviews:

A previous review M Kato 2021(13) found that relapse rates can be reduced to 20% by continuation of the same antidepressant medication used to achieve remission, relapse rate remained unchanged from 6 months to over 1 year in both the antidepressant and placebo groups. Neither group had an increase in relapse rate after 6 months, so more attention may be needed on the relapse rate in the first 6 months rather than 6 months after remission. It recommends continuing maintenance therapy, and careful attention for at least 6 months after remission to prevent relapse and treatment failure. This review did not make any evaluation regarding pharmacologic withdrawal of antidepressants because relapse and dropout rates in the short 4–8 weeks could not be assessed in this review. Subanalysis in this review showed that dropout rates did not change in abrupt discontinuation trials and that withdrawal symptoms did not affect relapse in the short-term results.
Our review (with meta-analysis) provides insufficient evidence to suggest that discontinuation of antidepressants is safe and effective compared to continuation after remission in individuals who

have taken antidepressants for a period of 3 to 6 months. It is difficult to draw any concrete conclusion in this review because of potential risk of bias due to not measurement of withdrawal symptoms in all included studies except one.
Guidelines recommend continuing antidepressant therapy for at least 6 months after successful acute phase treatment to prevent relapse/recurrence and up to 1 years in case of recurrent depression. (8), (9), (10) but there is a lack of evidence for the optimal duration of continuation and maintenance treatment, most guidelines are based on expert opinion and consensus.
One previous review Van Leeuwen 2021(4) also found out that none of included trials reported successful discontinuation rate as a primary endpoint. This is analogues with the results in our review. This previous review Van Leeuwen 2021 (4) compared different approaches to discontinuation with continuation of antidepressants six months after stabilization but could not provide any concrete conclusion. In this review we did not compare other approaches of discontinuation, for example, Discontinuation by "taper", Discontinuation with psychological support, Discontinuation with minimal intervention. In our review we included only studies with discontinuation of antidepressant. Therefore, we cannot comment on these findings.

6. Author's conclusions:

We present following key messages for practice and research.

Implications for practice:

This new review (with meta-analysis) provides insufficient evidence to suggest that discontinuation of antidepressants is safe and effective compared to continuation after remission in individuals who have taken antidepressants for a period of 3 to 6 months after remission. Therefore, unsupervised abrupt discontinuation after 3-6 months of stabilization is probably not a viable approach.

Implications for research:

In future research there is a need for reliable and specific studies with focus on different discontinuation strategies with successful discontinuation as the primary endpoint and a clear distinction between relapse and withdrawal symptoms.

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8.Appendices :

8.1. Abbreviations:

CGI	Clinical Global Impression
DSM	Diagnostic and Statistical Manual of Mental Disorders
HAM-A	Hamilton Anxiety Scale
HAMD	Hamilton Rating Scale for Depression
MADRS	Montgomery-Åsberg Depression Rating Scale
SDS	Sheehan Disability Scale
AD	Abbreviation Antidepressant
SSRI	Selective Serotonin Reuptake Inhibitors
TCA	Tricyclic Agent

9. Characteristics of studies

Characteristics of included studies

Alexopoulos 2000

Methods	**Design:** RCT **Prerandomisation phase:** - A total of 100 elderly subjects received open acute nortriptyline treatment (duration not mentioned) - 58 patients received 16 weeks continuation nortriptyline treatment Duration post randomisation: 2 years **Method:** Fifty-eight elderly subjects remitted from major depression received continuation nortriptyline treatment (plasma levels 60-150 ng/mL) for 16 weeks and then were randomly assigned to either nortriptyline maintenance therapy or placebo for up to 2 years. Diagnosis was made using the Research Diagnostic Criteria and the DSM-IV criteria after an interview using the Schedule for Affective Disorders and Schizophrenia. Executive dysfunction and memory were assessed with the Dementia Rating Scale, disability and social support were rated with the Philadelphia Multiphasic Instrument, and medical burden was assessed with the Cumulative Illness Rating Scale. **Aim:** This study investigated the relationship of executive and memory impairment to relapse, recurrence, and course of residual depressive symptoms and course of residual depressive symptoms and signs after remission of geriatric major depression.
Participants	**Country:** USA **Setting:** Ambulant patients of department of psychiatry, Cornell university white plains NY. To increase protocol adherence, only subjects residing within a 45-minute drive from the hospital were selected. All subjects were required to have informants who had knowledge of the subject's history and enough contact so that they could observe changes within a week. Subjects and informants provided written informed consent. **Type of AD:** Nortriptyline **Duration of antidepressant treatment pre randomisation:** A total of 100 elderly subjects received open acute nortriptyline treatment (duration not mentioned) -58 patients received 16 weeks continuation nortriptyline treatment after remission **Duration of antidepressant treatment post stabilisation**: 2 years nortriptyline maintenance therapy **Total number of randomised participants**: 43 (21 placebo, 22 antidepressant) Of the 57 subjects who completed the continuation phase, 43 agreed to participate in the maintenance phase and were randomly assigned either to nortriptyline or placebo. Of the 43 subjects who entered the maintenance phase, 22 continued to receive nortriptyline and 21 were switched to placebo. **Primary diagnosis:** unipolar major depression without psychotic features.

	Severity of depressive symptoms at randomisation, mean (SD) HDRS score of 10 or lower and a Cornell Scale34 score of 6 or lower for 3 consecutive weeks. Cornell Scale scores of 6 and lower discriminate depressed from non-depressed elderly patients. Comorbidity: The clinical characteristics of these patients suggest that when symptomatic they had moderate to severe depression and a wide range of cognitive impairment, medical comorbidity, disability and social support . **Gender distribution (F):** 64.9 is continuation phase and 62.8 percent in maintenance phase **Mean age, years (SD):** 65 plus **Definition of remission**: The subjects were considered in remission if they no longer met RDC research diagnostic criteria)criteria for depression and had an HDRS score of 10 or lower and a Cornell Scale34 score of 6 or lower for 3 consecutive weeks. Cornell Scale scores of 6 and lower discriminate depressed from non-depressed elderly patients. **Inclusion criteria** Fifty-eight elderly subjects remitted from major depression received continuation nortriptyline treatment (plasma levels 60-150 ng/mL) for 16 weeks and then were randomly assigned to either nortriptyline maintenance therapy or placebo for up to 2 years. Diagnosis was made using the Research Diagnostic Criteria and the DSM-IV criteria after an interview using the Schedule for Affective Disorders and Schizophrenia. Executive dysfunction and memory were assessed with the Dementia Rating Scale, disability and social support were rated with the Philadelphia Multiphasic Instrument, and medical burden was assessed with the Cumulative Illness Rating Scale. The subjects had met Research Diagnostic Criteria (RDC)30 and DSM-IV criteria31 for unipolar major depression without psychotic features, had a score of 19 or greater on the 24-item Hamilton Depression Rating Scale (HDRS),32 and a score of 1 (absent) on the Delusions and Hallucinations items of the Schedule for Affective Disorders and Schizophrenia–Lifetime Version (SADS-L).33 **Exclusion criteria** Depressed patients were excluded if they had (1) history of other psychiatric disorders (except personality disorders) prior to their depression; (2) severe or acute medical illness (e.g., metastatic cancer, brain tumour, decompensated cardiac, hepatic, or renal failure, or myocardial infarction or stroke within the 3 months preceding the study); (3) neurological disorders (e.g., delirium, Parkinson disease, or multiple sclerosis); (4) conditions and drugs that may cause depression (endocrinopathies other than diabetes, lymphoma, or pancreatic cancer, or the use of steroids, β-blockers, α-methyl-dopa, clonidine, reserpine, tamoxifen, or cimetidine); or (5) Mini-Mental State Examination35 score of less than 17. Therefore, the subjects were non delusional depressed elderly patients with a wide range of cognitive impairment
Interventions	**Intervention 1:** placebo Intervention 2: continuation of the same dose of amitriptyline. The night-time daily dose was 138 mg (range 50 to 250 mg)
Outcomes	Diagnosis was made using the Research Diagnostic Criteria and the DSM-IV

	criteria after an interview using the Schedule for Affective Disorders and Schizophrenia. The subjects were considered in remission if they no longer met RDC research diagnostic criteria) criteria for depression and had an HDRS score of 10 or lower and a Cornell Scale score of 6 or lower for 3 consecutive weeks. Cornell Scale scores of 6 and lower discriminate depressed from non-depressed elderly patients. Executive dysfunction and memory were assessed with the Dementia Rating Scale, disability and social support were rated with the Philadelphia Multiphasic Instrument, and medical burden was assessed with the Cumulative Illness Rating Scale.
Notes	**Funding:** not described **COI:** not described

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	subjects were assigned either to nortriptyline (plasma levels 60-150 ng/mL) or to placebo maintenance treatment for 2 years using random computer numbers, and were followed up under double-blind conditions
Allocation concealment (selection bias)	Low risk	subjects were assigned either to nortriptyline (plasma levels 60-150 ng/mL) or to placebo maintenance treatment for 2 years using random computer numbers, and were followed up under double-blind conditions
Blinding of participants and personnel (performance bias)	Low risk	subjects were assigned either to nortriptyline (plasma levels 60-150 ng/mL) or to placebo maintenance treatment for 2 years using random computer numbers, and were followed up under double-blind conditions
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Unclear risk	Not reported
Selective reporting (reporting bias)	High risk	No discontinuation symptoms mentioned. withdrawal symptoms were not reported.
Other bias	Unclear risk	Funding: not described COI: not described

Allgulander 2006

Methods	**Design:** RCT **Prerandomisation phase:** 12 wk of open-label treatment **Duration post randomisation:** 24-76 weeks double blinded placebo vs **escitalopram phase** Patients were in the double blind period for a minimum of 24 wk and a maximum of 76 wk if they remained well, depending on when in the recruitment period they entered the study, as all patients completed the double-blind period on the same date.

	Method of recruitment: Patients were recruited by general practitioners, by psychiatrists; some used media advertisements. **Aim:** To evaluate the effect of escitalopram (20 mg/d) vs. that of placebo on the prevention of relapse of GAD in patients who had responded to treatment with escitalopram
Participants	**Country:** The study was conducted in 59 centres in eight countries in accordance with the principles of Good Clinical Practice (ICH, 1996) and the Declaration of Helsinki (WMA, 2000) applicable at the time of the study. The study was approved by the relevant local ethics committees and all patients gave their written informed consent Setting: Patients eligible for this study were outpatients with a primary diagnosis of GAD according to DSM-IVTR criteria (APA, 2000) who were otherwise healthy. **Type of AD:** Escitalopram **Duration of antidepressant treatment pre randomisation:** 12 wk of open-label treatment **Duration of antidepressant treatment post stabilisation:** 24-76 weeks double blinded placebo vs escitalopram phase Patients were in the double blind period for a minimum of 24 wk and a maximum of 76 wk if they remained well, depending on when in the recruitment period they entered the study, as all patients completed the double-blind period on the same date. Total number of randomised participants: 375 (188placebo, 187 antidepressant) **Primary diagnosis:** GAD Severity of depressive symptoms at randomisation, mean (SD) HAMA total score<or=10 Comorbidity: not described Gender distribution (F): 60 % females Mean age, years (SD): 40 Definition of remission: at randomisation, mean (SD) HAMA total score<or=10 **Inclusion criteria** Patients eligible for this study were outpatients with a primary diagnosis of GAD according to DSM-IVTR criteria (APA, 2000) who were otherwise healthy and who had given informed consent. Patients aged 18–65 years were eligible if they had a HAMA total score of 20 and a score of 2 on both HAMA item 1 (anxious mood) and item 2 (tension) at screening as well as at the start of the open-label period. To rule out comorbid depressive disorder, only patients who had a low level of depressive symptoms were allowed in the study; a Montgomery – Asberg Depression Rating Scale (MADRS; Montgomery and A˚ sberg, 1979) score of f16 at screening and at the start of open-label period. **Exclusion criteria** Patients with any of the following DSM-IV disorders elicited with the MINI (Sheehan et al., 1998) were excluded: major depressive disorder, panic disorder, social anxiety disorder, post-traumatic stress disorder, bipolar disorder, obsessive–compulsive disorder, eating disorders, substance use

	disorder, and any current or past psychotic disorder. Patients were also excluded if they had a body dysmorphic disorder or any personality disorder, were at risk of suicide (elicited in the MINI, or had >3 points on item 10 'suicidal thoughts' of the MADRS), or had made a suicide attempt within the past year. Furthermore, patients with an unstable serious somatic illness and/or serious sequelae of liver or renal insufficiency were also excluded. Pregnant or breastfeeding women were excluded.
Interventions	**Intervention 1:** placebo **Intervention 2:** Escitalopram
Outcomes	Remission was defined as HAMA total score<or=10 The primary efficacy parameter was the time to relapse during the double-blind treatment period. Relapse was defined as an increase in HAMA total score to o15 (Montgomery and van Zwieten-Boot, 2002) or lack of efficacy as judged by the investigator. Only 12 patients were withdrawn for lack of efficacy as judged by the investigator. The secondary efficacy parameters included change in scores from the following scales: the HAMA total, HAMA psychic anxiety sub scale (items 1–6, 14) and the HAMA somatic anxiety sub scale (items 7–13), MADRS, Hospital Anxiety and Depression Anxiety (HADA) sub scale scores (Zigmond and Snaith, 1983), Clinical Global Impressions – Severity of illness (CGI-S) and Improvement of illness (CGI-I; Guy, 1976), and the Sheehan Disability Scale (SDS; Sheehan, 1983) scores (work, social life, and family life). Clinical research staff were trained using videotaped interviews of GAD patients. Inter-rater agreement was assessed, and if ratings fell outside acceptable limits, further training was given. Only those subsequently approved as raters were allowed to rate patients. The tolerability and safety evaluations were based on spontaneously reported adverse events (AEs), vital signs, body weight, physical examinations, and clinical safety laboratory tests. If AEs were contributory to withdrawal from the study, they were regarded as the primary reason for withdrawal. Discontinuation symptoms were assessed by evaluation of AEs during the 2-wk taper period (tapering of escitalopram for patients randomised to the placebo arm) and during the 2-wk taper period for patients who completed the study.
Notes	**Funding:** not described **COI:** not described

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients who responded to treatment were randomised to double blind treatment in a 1: 1 ratio, using a computer generated randomisation list, with either 20 mg/d escitalopram or placebo
Allocation concealment (selection bias)	Low risk	Patients who responded to treatment were randomised to double blind treatment in a 1: 1 ratio, using a computer generated randomisation list, with either 20 mg/d escitalopram or placebo
Blinding of participants	Low risk	Patients who responded to treatment were randomised

and personnel (performance bias)		to double blind treatment in a 1: 1 ratio, using a computer generated randomisation list, with either 20 mg/d escitalopram or placebo
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Unclear risk	Not described
Selective reporting (reporting bias)	Low risk	discontinuation symptoms mentioned. withdrawal symptoms are reported.
Other bias	Unclear risk	**Funding:** not described **COI:** not described

Baldwin 2012

Methods	**Design:** RCT **Prerandomisation phase**: 20 weeks open label (Flexible dose for first 8 weeks en a fixed dose from week 8) **Duration post randomisation**: 24-56 weeks double blind RCT phase **Aim:** The purpose of this study was to investigate the long-term maintenance of the efficacy of Lu AA21004 5 or 10 mg/day in the prevention of relapse in patients with generalized anxiety disorder (GAD).
Participants	**Country And Setting:** This double-blind, randomised, placebo-controlled relapse- prevention study recruited 687 outpatients from 80 centres in 10 countries (Argentina, Chile, Colombia, Costa Rica, Estonia, Finland, France, Hungary, Russian Federation and South Africa) **Type of AD:** Lu AA21004 **Duration of antidepressant treatment pre randomisation**: 20 weeks open label **Duration of antidepressant treatment post stabilisation:** 24-56 weeks double blind RCT phase Total number of randomised participants: 459 patients (67%) were randomised to double-blind treat- ment: 230 patients to placebo and 229 patients to Lu AA21004 Primary diagnosis: GAD (DSM-IV criteria) Severity of depressive symptoms at randomisation, mean (SD) , HAMA total score< or =10 Average age of onset of depressive disorder: aged from 18 to 75 years. Hamilton Anxiety Scale (HAM-A); Hamilton, 1959, total score r 10 **Comorbidity:** not described **Gender distribution (F):** not described **Definition of remission:** HAMA total score< or =10 **Inclusion criteria** Patients with a primary diagnosis of GAD according to the DSM-IV-TR criteria (American Psychiatric Association, 2000) were included in the trial if they were an outpatient of either sex, aged from 18 to 75 years. Only patients with a HAM-A total score of at least 20, a HAM- A score of at least 2 on item 1 (anxious mood) and 2 (tension) and a Montgomery–Å sberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) total

	score of 16 or less at both the screening and the baseline visits were included. **Exclusion criteria** Patients were excluded if they had any current psychiatric disorder other than GAD as defined in the DSM-IV- TR [assessed using the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998)] or a current or past medical history that might compromise the study, as described in Boulenger et al. (in press), or any substance abuse disorder (except nicotine and caffeine) within the previous 6 months. Patients at serious risk of suicide, on the basis of the investigator's clinical judgement, or who had a score of at least 5 on item 10 of the MADRS scale (suicidal thoughts) were also excluded, as were those who were pregnant or breast-feeding or whose current GAD symptoms were considered by the investigator to have been resistant to two adequate antidepressant treatments of at least 6 weeks' duration, or who had previously been exposed to Lu AA21004. Patients were excluded if they had received electroconvulsive therapy within 6 months before screening, were currently receiving formal cognitive or behavioural therapy, systematic psychotherapy, or planned to initiate such therapy during the study, or if they had a clinically significant unstable illness, or clinically significant abnormal vital signs or ECGs. Patients were also excluded if they were taking any of the drugs specified previously (Boulenger et al., in press) within 2 weeks before baseline or during the study.
Interventions	**Intervention 1**: placebo **Intervention 2:** Lu AA21004 **Co-intervention:** Not described
Outcomes	The predefined primary efficacy endpoint was time to relapse (HAM-A total score Z 15) using a Cox model the key secondary efficacy endpoint under multiplicity control was time to relapse for patients responding to treatment for at least 12 weeks.
Notes	**Funding:** not described **COI:** not described

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients who fulfilled the randomization criteria after the completion of the open-label period were assigned in a 1 : 1 ratio to treatment with either Lu AA21004 or placebo, using an interactive voice response system, in accordance with a computer-generated randomization list hosted by H. Lundbeck A/S. The details of the randomization series were unknown to the investigators. Randomization in blocks of four ensured that equal numbers of patients entered each treatment group. All investigators, trial personnel and participants were blinded to treatment assignment for the duration of the entire study. The randomization code was not broken for any patient during the study.
Allocation	Low risk	Patients who fulfilled the randomization criteria after the

concealment (selection bias)		completion of the open-label period were assigned in a 1 : 1 ratio to treatment with either Lu AA21004 or placebo, using an interactive voice response system, in accordance with a computer-generated randomization list hosted by H. Lundbeck A/S. The details of the randomization series were unknown to the investigators. Randomization in blocks of four ensured that equal numbers of patients entered each treatment group. All investigators, trial personnel and participants were blinded to treatment assignment for the duration of the entire study. The randomization code was not broken for any patient during the study.
Blinding of participants and personnel (performance bias)	Low risk	Patients who fulfilled the randomization criteria after the completion of the open-label period were assigned in a 1 : 1 ratio to treatment with either Lu AA21004 or placebo, using an interactive voice response system, in accordance with a computer-generated randomization list hosted by H. Lundbeck A/S. The details of the randomization series were unknown to the investigators. Randomization in blocks of four ensured that equal numbers of patients entered each treatment group. All investigators, trial personnel and participants were blinded to treatment assignment for the duration of the entire study. The randomization code was not broken for any patient during the study.
Blinding of outcome assessment (detection bias)	Low risk	study is described as double-blinded, and blinding appeared to be maintained
Incomplete outcome data (attrition bias)	Unclear risk	No missing outcome data see fig 2 page 201
Selective reporting (reporting bias)	High risk	No discontinuation symptoms mentioned. withdrawal symptoms were not reported.
Other bias	Unclear risk	Funding not described

Boulenger 2012

Methods	Design: RCT Prerandomisation phase: The study consisted of two consecutive periods: a 12-week, open label, flexible-dose treatment period with Lu AA21004 **Duration post randomisation:** and a double-blind, fixed-dose, placebo-controlled treatment period of 24–64 weeks **Aim**: Lu AA21004 in the prevention of relapse in patients with major depressive disorder
Participants	**Country and Setting:** This double-blind, randomised, placebo-controlled, relapse-prevention study recruited 639 in- and outpatients from 66 psychiatric settings in 17 countries (Australia, Austria, Belgium, Canada, Finland, France, Germany, India, the Republic of Korea, Norway, Poland, South Africa, Sweden, Taiwan, Thailand, Turkey and the United Kingdom). Patients with major depressive disorder (MDD) were recruited from psychiatric settings from December 2007 to September 2009.

	Advertisements were used to recruit patients in Australia, Austria, Canada, Finland, Germany, the Republic of Korea, South Africa, Sweden and Taiwan. The trial was conducted in accordance with the principles of Good Clinical Practice (ICH, 1996) and the Declaration of Helsinki (World Medical Association, 1964, and its amendments in force at the initiation of the study) Local ethics committees approved the trial design and eligible patients gave their written informed consent before participating. **Type of AD:** Lu AA21004 **Duration of antidepressant treatment pre randomisation:** a 12-week, open label, flexible-dose treatment period with Lu AA21004 **Duration of antidepressant treatment post stabilisation**: not reported Total number of randomised participants: **Patients randomised n** = 400 Placebo n = 194 (FAS n = 192) (FAS n = 204) **Primary diagnosis:** major depressive disorder (MDD) **Severity of depressive symptoms at randomisation, mean (SD**) Patients in remission (MADRS total score ≤10) **Average age of onset of depressive disorder**: 18 to 75 years **Comorbidity**: Not reported **Gender distribution (F):** Approximately two-thirds of the patients were female, the average age was 45 years, **Mean age, years (SD):** 45 years **Definition of remission**: Patients in remission (MADRS total score ≤10) **Inclusion criteria** 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 were also excluded if they were taking any of the following drugs within two weeks prior to baseline or during the study: any investigational drug, narcotic analgesics, anorexics, anticonvulsants, antidepressants (including MAOIs and RIMAs), psychoactive herbal remedies, antidiarrhoeal agents, antihistamines, antimigraine agents, antiemetics, anti obesity agents, antipsychotics, anxiolytics (including benzodiazepines), cough or cold agents, diuretics, systemic steroids, mood stabilizers, sedatives or hypnotics and episodic use of insulin, hypoglycaemic agents and hormones. Episodic use of zolpidem, zopiclone, or zaleplon for insomnia (for a maximum of two days per week, but not the night before a study visit), of antidiarrhoeal agents loperamide, bismuth and kaolin preparations, of antihistamines loratadine, desloratadine and cetirizine, cough or cold agents (except preparations with pseudoephedrine or narcotics), anticoagulants (including aspirin), NSAIDs and diuretics was allowed. 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 randomisation 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, hospitalisation) 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
Interventions	**Intervention 1:** placebo **Intervention 2:** Lu AA21004 **Co-intervention:** Not Reportd
Outcomes	1- Time to relapse (full-analysis set, Cox proportional hazard model) showed a statistically significant difference in favour of Lu AA21004 versus placebo with a hazard ratio of 2.01 (95% confidence interval: 1.26–3.21; p=0.0035). The proportion of patients who relapsed was 13% in the Lu AA21004 group (n=27) and 26% in the placebo group (n=50). 2-The withdrawal rates due to adverse events were 8% (open-label), and 3% (placebo) and 8% (Lu AA21004) (double-blind).
Notes	Funding: This work was supported by H Lundbeck A/S. COI: J-PB is a consultant for, has received honoraria from and has conducted clinical research supported by H Lundbeck A/S. HL and IF are employed by H Lundbeck A/S.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	Patients who fulfilled the randomization criteria after completion of the open-label period were assigned to

(selection bias)		treatment with either Lu AA21004 or placebo, in accordance with a computer-generated randomization list by H Lundbeck A/S. The details of the randomization series were unknown to any of the investigators and were contained in a set of sealed opaque envelopes. At each study centre, sequentially enrolled patients were assigned the lowest randomization number available in blocks of four. All investigators, trial personnel and participants were blinded to treatment assignment for the duration of the entire study. The randomization code was accidentally broken for three patients, who were withdrawn from the study, and intentionally broken for another two patients after they had relapsed and had been withdrawn from the study.
Allocation concealment (selection bias)	Low risk	Patients who fulfilled the randomization criteria after completion of the open-label period were assigned to treatment with either Lu AA21004 or placebo, in accordance with a computer-generated randomization list by H Lundbeck A/S. The details of the randomization series were unknown to any of the investigators and were contained in a set of sealed opaque envelopes. At each study centre, sequentially enrolled patients were assigned the lowest randomization number available in blocks of four. All investigators, trial personnel and participants were blinded to treatment assignment for the duration of the entire study. The randomization code was accidentally broken for three patients, who were withdrawn from the study, and intentionally broken for another two patients after they had relapsed and had been withdrawn from the study.
Blinding of participants and personnel (performance bias)	Low risk	Patients who fulfilled the randomization criteria after completion of the open-label period were assigned to treatment with either Lu AA21004 or placebo, in accordance with a computer-generated randomization list by H Lundbeck A/S. The details of the randomization series were unknown to any of the investigators and were contained in a set of sealed opaque envelopes. At each study centre, sequentially enrolled patients were assigned the lowest randomization number available in blocks of four. All investigators, trial personnel and participants were blinded to treatment assignment for the duration of the entire study. The randomization code was accidentally broken for three patients, who were withdrawn from the study, and intentionally broken for another two patients after they had relapsed and had been withdrawn from the study.
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Unclear risk	Not described

Selective reporting (reporting bias)	High risk	withdrawal symptoms were not reported.
Other bias	Unclear risk	Funding: This work was supported by H Lundbeck A/S. COI: J-PB is a consultant for, has received honoraria from and has conducted clinical research supported by H Lundbeck A/S. HL and IF are employed by H Lundbeck A/S.

Davidson 2008

Methods	**Design:** RCT **Pre randomisation phase:** 26-week open-label, flexible-dose acute-therapy phase with duloxetine . **Duration post randomisation**: 26-week double-blind, placebo-controlled continuation therapy phase The study also had a screening and a 3-week taper/follow-up therapy phase. **Aim:** The objective was to examine duloxetine 60–120 mg/day treatment for relapse prevention in adults with generalized anxiety disorder (GAD)
Participants	**Country:** Male and female patients aged ≥ 18 years were recruited globally from outpatient psychiatric clinics and university settings (28 sites throughout Austria, France, Germany, Portugal, and the Netherlands and 22 sites in the United States) Setting: outpatient psychiatric clinics and university settings **Type of AD:** Duloxetine. **Duration of antidepressant treatment pre randomisation**: 26-week open-label, flexible-dose acute-therapy phase with duloxetine . **Duration of antidepressant treatment post stabilisation**: 26 week double-blind, placebo-controlled continuation therapy phase. **Total number of randomised participants**: 429 (213 placebo, 216 antidepressant) **Primary diagnosis**: GAD **Severity of depressive symptoms at randomisation, mean (SD)** Responder status was required for the last 2 consecutive visits of the open-label trial and was defined as a ≥ 50% reduction in Hamilton Anxiety Rating Scale (HAMA; Hamilton, 1959) total score from baseline to a score ≤ 11 and a CGI-I rating of “very much” or “much improved” Comorbidity: not described **Gender distribution (F):** 61.1% females AD 58.7 females % placebo **Mean age, years (SD):** 45 **Definition of remission: at randomisation, mean (SD)** (HAMA; Hamilton, 1959) total score from baseline to a score ≤ 11 and a CGI-I rating of “very much” or “much improved” **Inclusion criteria:** Patients had to meet theDiagnostic and Statistical Manual of Mental Disorders, IV edition,text-revision criteria for GAD (DSM-IV-TR; APA, 2000), which were assessed via the Mini International Neuropsychiatric Interview for the DSM (MINI; Sheehan et al., 1998) and confirmed by study psychiatrist. Patients' illness had to be at least moderately severe as indicated by a Clinical Global Impressions Severity (CGI-S; Guy,

	1976a) rating of ≥4 (moderate), a Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983) anxiety sub scale score ≥10, and a Covi Anxiety Scale (CAS; Lipman and Covi, 1976) score ≥ 9. Toensure predominance of anxiety symptoms, none of the 5 items on the Raskin Depression Rating scale (RDR; Raskin et al., 1969) could be scored N3, and the CAS score had to be greater than the RDR total. **Exclusion criteria** Patients were not eligible to participate in the study if they met any of the following diagnoses: current or previous 6-month diagnosis of major depressive disorder, or substance abuse or dependence; a past year history of panic disorder, posttraumatic stress disorder, or an eating disorder; or a lifetime diagnosis of obsessive–compulsive disorder, bipolar affective disorder, psychosis, factitious disorder, or somatoform disorder. They were excluded if they were taking psychotropic medications within 7 days before baseline (14 days for benzodiazepines and 4 weeks for fluoxetine or a monoamine oxidase inhibitor), consuming excessive caffeine per investigator judgment, or had any medical condition that would contraindicate taking duloxetine. Women who were breastfeeding or pregnant were not allowed to participate, and women of child-bearing potential were required to use reliable methods of birth control. Patients who had a prior treatment history with duloxetine or whose GAD had failed to respond to 2 adequate trials of pharmacological treatment per the treating physician were ineligible as well.
Interventions	**Intervention 1:** placebo **Intervention 2:** Duloxetine.
Outcomes	The primary efficacy measure was the time to relapse during the 26-week double-blind continuation therapy phase. Relapse was defined as an increase in the CGI-S rating of at least 2 points from randomisation (end of open-label phase) to a score ≥ 4 (moderate) while meeting criteria for GAD confirmed by the MINI or by discontinuation due to lack of efficacy. The secondary efficacy measure was the HAMA total score, which was administered using the Structured Interview Guide for the HAMA version (SIGH-A; Shear et al., 2001). The HAMA is a clinician-rated instrument consisting of 14 items that are rated on a 0 (“not at all”) to 4 (“very severe/disabling”) scale; higher total scores indicate greater distress and impairment. The SIGH-A version specifies instructions for administration and scoring based on frequency, severity, and impairment of symptoms and has been demonstrated to increase reliability (Shear et al., 2001). Study personnel involved in assessing patients were required to obtain sponsor approval, which was based on their demonstrating interviewing competence via mock interviews and scoring reliability via a videotaped interview. The intra class correlation coefficient for the HAMA total score was 0.91 for the training tape and 0.87 for a re calibration tape during the study; both values indicate excellent interrater reliability.

	Additional outcome measures included the HAMA psychic factor score (sum items 1–6, 14) and the HAMA somatic factor scores (sum of items 7–13). Patients completed the 14-item HADS, which consists of separate sub scale (7 items each) for anxiety and depression; higher scores indicate greater symptom frequency or distress. Overall improvement was rated by clinicians using the CGI-I and by the patients using the Patient Global Impressions of Improvement (PGI-I; Guy, 1976b). Ratings for these scales range from 1 to 7, in which lower scores indicate greater improvement. CGI-I and CGI-S ratings were required to be completed by a physician who had at least 1 year experience in the treatment of patients with anxiety disorders. Role functioning was assessed by the Sheehan Disability Scale (SDS; Sheehan, 1983), in which patients rated their degree of impairment using a 10-point scale from 0 (“none”) to 10 (“extremely disabling”) for 3 life domains: work/school, social life, and family/home responsibilities. The global functioning impairment score is the sum of the 3 items, and global scores > 5 have been shown to indicate impairment associated with psychiatric illness (Leon et al., 1997). Patients' satisfaction with their lives and perceived health were measured by the Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF; Endicott et al., 1993) and the European Quality of Life: 5 Dimensions Visual Analogue Scale (EQ-5D VAS; EuroQol, 1990). Tolerability of study medication was assessed by spontaneously reported adverse events (AEs) and reasons for study discontinuation. At each visit, clinicians also completed the Beck Scale for Suicidal Ideation (BSSI; Beck et al., 1979), which has an initial screening question; positive responses to the screening are followed by detailed assessment of a patient's behaviours, attitudes, and plans to commit suicide. Although any positive score on this scale has been associated with increased risk for suicidal behaviours, a score of ≥ 6 has been used to denote at least moderate ideation and significant risk for suicidal behaviours (Sokero et al., 2003). Vital signs were also collected at each visit.
Notes	**Funding**: Research funded by Eli Lilly and Company and Boehringer Ingelheim GmbH. **COI:** This research was funded by Eli Lilly and Company and Boehringer Ingelhem GmbH. Funding support included personnel and materials involved in study design; collection, analysis and interpretation of data; and the writing of the report

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	actual double-blind assignment of treatment occurred at week 26 in a 1:1 ratio and was administered via an interactive voice recognition system. Patients who were randomly assigned to placebo underwent a 2-week taper of study medication, while those assigned to duloxetine were continued at the same dose as their open-label phase treatment. All doses were taken once daily, and to maintain the blind, all patients received 4 capsules throughout the double-blind phase.
Allocation concealment (selection bias)	Low risk	actual double-blind assignment of treatment occurred at week 26 in a 1:1 ratio and was administered via an interactive voice recognition system. Patients who were randomly assigned to placebo underwent a 2-week taper of study medication, while those assigned to duloxetine were continued at the same dose as their open-label phase treatment. All doses were taken once daily, and to maintain the blind, all patients received 4 capsules throughout the double-blind phase.
Blinding of participants and personnel (performance bias)	Low risk	the actual double-blind assignment of treatment occurred at week 26 in a 1:1 ratio and was administered via an interactive voice recognition system. Patients who were randomly assigned to placebo underwent a 2-week taper of study medication, while those assigned to duloxetine were continued at the same dose as their open-label phase treatment. All doses were taken once daily, and to maintain the blind, all patients received 4 capsules throughout the double-blind phase.
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Unclear risk	The results of the present study should also be evaluated in the context of a few limitations. As noted, attrition occurred throughout the study, which may limit the

		generalisation of the findings. Secondly, the patients were selected for having primary GAD without significant comorbidity. Because GAD is frequently comorbid with both anxiety and affective disorders, the findings may not generalize to the clinical patient who has substantial comorbidity among the different disorders.
Selective reporting (reporting bias)	High risk	No discontinuation symptoms mentioned. withdrawal symptoms were not reported.
Other bias	Unclear risk	**Funding:** Research funded by Eli Lilly and Company and Boehringer Ingelheim GmbH. **COI:** This research was funded by Eli Lilly and Company and Boehringer Ingelhem GmbH. Funding support included personnel and materials involved in study design; collection, analysis and interpretation of data; and the writing of the report

Dinan 2001

Methods	Design: RCT Prerandomisation phase: 13 weeks open label acute treatment Duration post randomisation: 25 weeks double-blind treatment in 3 groups Fluoxetine weekly, fluoxetine daily, placebo Aim: To see Efficacy and safety of weekly treatment with enteric-coated fluoxetine in patients with major depressive disorder
Participants	Country: not described Setting: Not described Type of AD: Fluoxetine **Duration of antidepressant treatment pre randomisation**: 13 weeks **Duration of antidepressant treatment post stabilisation:** 25 weeks double-blind treatment **Total number of randomised participants**: 501 190 in fluoxetine weekly 189 fluoxetine daily 122 placebo **Primary diagnosis**: MDD **Severity of depressive symptoms at randomisation, mean (SD)** Comorbidity: not described **Gender distribution (F):** not described **Mean age, years (SD):** 18-75

	Definition of remission at randomisation, mean (SD) No longer meeting DSMIV criteria for an MDE ,with a HAM-D17 score< or =9 and a CGI score <or=2 **Inclusion criteria:** Adults from age 18 -80 years from either sex with non psychotic major depression for at least 4 weeks were included. the current episode was required to be of moderate severity **Exclusion criteria:** Previous non responders to fluoxetine Current treatment resistance
Interventions	**Intervention 1:** placebo **Intervention 2:** Fluoxetine
Outcomes	Efficacymeasures included diagnosis of relapse (Meeting criteria for an MDE as determined by SCID-P MDEmodule,with a CGI-S score increase >2 relative to the rating at visit 9 for 2 consecutive visits.)as wells as modified HAM-D 17, HAM-D-28 sub scales and CGI scores. The HAM-D28 sub scales included the core total (item 1,2,3,7and8) sub scale 5 (items 1,2,3,7,8,14,15,16 and 17) anxiety (items 10,11,12,13,15 and 17) depressed mood (item 1) sleep (item 4,5,and6) and retardation (item 1,7,8and 14 scales
Notes	**Funding:** not described **COI:** not described

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported how patients are randomised
Allocation concealment (selection bias)	Unclear risk	Method Not described
Blinding of participants and personnel (performance bias)	Unclear risk	Method Not described
Blinding of outcome assessment (detection bias)	Unclear risk	Method Not described
Incomplete outcome data (attrition bias)	Unclear risk	Not described
Selective reporting (reporting bias)	High risk	No discontinuation symptoms mentioned. withdrawal symptoms were not reported.
Other bias	Unclear risk	Funding: not described COI: not described

Durgam 2019

Methods	**Design:** RCT **Prerandomisation phase:** 20 weeks of open-label treatment

	Duration post randomisation: 26 weeks of double-blind treatment .` down-taper: 2 weeks Screening: 5 weeks This study was up to 53 weeks in duration and consisted of washout/screening; an open-label, flexible-dose, run-in phase (RIP); an open-label, fixed-dose, stabilization phase (SP); a double-blind treatment phase; and down-taper **Aim:** The current study was designed to evaluate the efficacy, safety, and tolerability of levomilnacipran ER in preventing relapse in adult patients with MDD.
Participants	**Country:** USA This was a multicenter, randomised, double-blind, placebo-controlled, relapse-prevention study with levomilnacipran ER in patients with MDD . The study was conducted from 2014 to 2016 at 44 study enters in the United States in full compliance with the International Council on Harmonisation guideline for Good Clinical Practice and the principles of the Declaration of Helsinki. T he protocol and amendments were approved by the institutional review board at each study centre, and all patients provided written informed consent. **Setting:** 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 **Type of AD**: Levomilnacipran **Duration of antidepressant treatment pre randomisation**: 20 weeks of open-label treatment **Duration of antidepressant treatment post stabilisation**: 26 weeks of double-blind treatment Total number of randomised participants: 324(159 placebo, 165antidepressant) **Primary diagnosis:** MDD **Severity of depressive symptoms at randomisation, mean (SD)** Montgomery-Åsberg Depression Rating Scale (MADRS) total score ≤12 Comorbidity: not described **Gender distribution (F**): 65.4 % females AD 69.1 females % placebo **Mean age, years (SD):** 46 years AD 44 years placebo **Definition of remission at randomisation, mean (SD)** Patients who completed the SP and met the following randomisation criteria were allowed to enter double-blind treatment: stable clinical response (MADRS total score ≤12 at weeks 8, 10, 12, 14, 16, 18, and 20; 1 or 2 modest excursions [i.e., MADRS total score > 12 but ≤16] at weeks 10, 12, or 14 were permitted); no significant tolerability issues as determined by the investigator; and no MADRS total score ≥17 at any time during the SP. **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/m2. **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); non response 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 Columbia-Suicide Severity Rating Scale. Concomitant treatment with psychoactive medications was prohibited, except for medications for insomnia.
Interventions	**Intervention 1**: placebo **Intervention 2:** Levomilnacipran
Outcomes	The primary efficacy parameter was time to first relapse during the double-blind treatment phase. Relapse was defined as meeting one or more of the following criteria: insufficient therapeutic response (e.g., ≥2-point increase from randomisation in Clinical Global Impression of Severity [CGI-S] (Guy, 1976) score, investigator-determined risk of suicide, need for hospitalisation due to worsening of depression, investigator-determined need for alternative antidepressant treatment) or an MADRS total score ≥18 at two consecutive visits occurring within 7 to 14 days. Additional efficacy parameters included CGI-Improvement (CGI-I; Guy, 1976) score relative to open-label baseline and changes from baseline or randomisation in MADRS total score, CGI-S score, and Sheehan Disability Scale (SDS; Sheehan, Harnett-Sheehan, & Raj, 1996) total and sub scale (work/school, social, and family) scores. AEs, serious AEs (SAEs), and vital signs were recorded at all study visits. Clinical laboratory tests and electrocardiograms were administered during screening, at randomisation, and at the end of double-blind treatment. The C-SSRS was administered at all study visits to monitor suicidal ideation or behavior.
Notes	**Funding:** The study was sponsored by the Forest Research Institute, an affiliate of Allergan (Madison, NJ). The sponsor was involved in the study design, collection, analysis and interpretation of data, and the decision to present these results. **COI:** not described

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	During the 26-week double-blind treatment, eligible patients were randomized (1:1) to placebo or levomilnacipran ER at the dose received during the SP. Randomization codes were generated electronically and implemented using an interactive web response system; identical packaging was used for all study medications. All patients, investigators, and the study sponsor were blinded to treatment assignment. Breaking the blind at the study center level disqualified the patient from further study participation.
Allocation concealment (selection bias)	Low risk	During the 26-week double-blind treatment, eligible patients were randomized (1:1) to placebo or levomilnacipran ER at the dose received during the SP. Randomization codes were generated electronically and implemented using an interactive web response system; identical packaging was used for all study medications. All patients, investigators, and the study sponsor were blinded to treatment assignment. Breaking the blind at the study center level disqualified the patient from further study participation.
Blinding of participants and personnel (performance bias)	Low risk	During the 26-week double-blind treatment, eligible patients were randomized (1:1) to placebo or levomilnacipran ER at the dose received during the SP. Randomization codes were generated electronically and implemented using an interactive web response system; identical packaging was used for all study medications. All patients, investigators, and the study sponsor were blinded to treatment assignment. Breaking the blind at the study center level disqualified the patient from further study participation.
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Unclear risk	Not described
Selective reporting (reporting bias)	High risk	No discontinuation symptoms mentioned. withdrawal symptoms were not reported.
Other bias	Unclear risk	Funding: The study was sponsored by the Forest Research Institute, an affiliate of Allergan (Madison, NJ). The sponsor was involved in the study design, collection, analysis and interpretation of data, and the decision to present these results. COI: not described

Fava 2002

Methods	**Design:** RCT **Prerandomisation phase:** 13 weeks open label acute treatment Duration post randomisation: **Continuation treatment:** 25 weeks double-blind treatment in 3 groups Fluoxetine weekly, fluoxetine daily, placebo 25-week double-blind rescue treatment: 25 weeks **Aim:** To assessed the response and the safety of reinitiating of treatment with a previously effective SSRI in depressed patients who relapse after discontinuation of treatment.
Participants	**Country:** not described **Setting**: This was a multicenter, double-blind, placebo-controlled, randomised study in which moderately depressed outpatients were started on a 13-week open-label daily treatment with 20 mg of fluoxetine. **Type of AD**: Fluoxetine **Duration of antidepressant treatment pre randomisation**: 13 weeks **Duration of antidepressant treatment post stabilisation**: 25 weeks double-blind treatment **Total number of randomised participants**: 501 in fluoxetine weekly: Not described in fluoxetine daily: Not described placebo:122 Primary diagnosis: Major depression **Severity of depressive symptoms at randomisation, mean (SD)** Modified HAMD17 score 9 and a CGI-Severity score 2 **Comorbidity:** Not described **Gender distribution (F):** 39 (70.9%) **Mean age, years (SD):** 40.9 **Definition of remission at randomisation, mean (SD)** Modified HAMD17 score 9 and a CGI-Severity score 2 **Inclusion criteria:** Men and women (18–80 years old) who met the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) [11] criteria for major depression of at least 1-month duration and had disease severity of at least moderate intensity (modified HAMD17 score of 618 and a CGI-Severity score 64) were eligible. Written informed consent was obtained from all the patients in accordance with the Helsinki conventions. The study protocol was approved by the Institutional Review Board of each of the 42 study centres **Exclusion criteria:** Not described
Interventions	**Intervention 1**: placebo

	Intervention 2: Fluoxetine
Outcomes	Response to the rescue treatment was defined as a ≥50% reduction in the modified HAMD17 score from the time of relapse and a CGI-Severity score of ≤2. The 17-item Hamilton was modified to give equal weight to typical and atypical neurovegetative symptoms and had been used in a previous study of the long-term efficacy of fluoxetine . Responders were seen monthly and could continue this treatment for up to 6 months after the point of relapse. Relapse during rescue treatment was defined as the investigator determining that a change in the antidepressant treatment was warranted. Safety measures were the evaluation of treatment-emergent adverse events, discontinuations for adverse events, and change in vital signs and clinical laboratory data.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not reported how randomisation is done
Allocation concealment (selection bias)	Low risk	study is described as double blinded and blinding is maintained
Blinding of participants and personnel (performance bias)	Low risk	study is described as double blinded and blinding is maintained
Blinding of outcome assessment (detection bias)	Unclear risk	insufficient information to permit judgment
Incomplete outcome data (attrition bias)	Unclear risk	insufficient information to permit judgment
Selective reporting (reporting bias)	High risk	No discontinuation symptoms mentioned. withdrawal symptoms were not reported.
Other bias	Unclear risk	insufficient information to permit judgment

Ferguson 2007

Methods	**Design:** RCT Prerandomisation phases: 2-week baseline phase, 12-week open label efficacy and safety phase, - Patients who completed the 12-week open-label treatment phase were considered responders and therefore eligible for the double blind continuation phase if they had ≤ 1 full-symptom panic attack per week during the last 2 weeks of open-label treatment and a Clinical Global Impressions Improvement (CGI-I) 57 score of 1 or 2 relative to their baseline score

	Duration post randomisation: 26-week **Aim:** to investigate the efficacy of continuation treatment in relapse prevention with venlafaxine ER versus placebo in outpatients who had responded to open-label venlafaxine ER treatment for panic disorder.
Participants	**Country:** Australia, Canada,Denmark, France, Hungary, Italy, Poland, and the United States **Setting:** outpatient treatment responders **Type of AD**: venlafaxine extended release (ER) **Duration of antidepressant treatment pre randomisation**: 12-week open-label treatment phase **Duration of antidepressant treatment post stabilisation**: 26-week *Number of participants: 313 patients entering the open-label period, 225 completed the open-label period, and 176 patients were randomised to maintenance treatment with venlafaxine ER(92 patients) or placebo (84 patients). **Total number of randomised participants:**176 (84 placebo, 92 antidepressant) Primary diagnosis: panic disorder with or without agoraphobia for at least 3 months before study day 1./ Severity of depressive symptoms at randomisation(mean, SD): Full-symptom panic attacks from PAAS (mean ± SD): placebo 0.37 ± 0.64, venlafaxine 0.34 ± 0.62 No. of full-symptom panic attacks, N (%)b: placebo 60 (71), venlafaxine 67 (74) PAAS = Panic and Anticipatory Anxiety Scale. **Comorbidity:** No **Gender distribution (F):** placebo 54 (64), venlafaxine 69 (75) **Mean age (year) (SD):** placebo 39.5 ± 10.7, venlafaxine 37.3 ± 10.9 **Inclusion criteria** - Outpatients aged ≥ 18 years who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for panic disorder with or without agoraphobia for at least 3 months before study day 1 (the first day of treatment) were eligible for the study. -Participants had to have a score a 4 on the Clinical Global Impressions-Severity of Illness (CGI-S)7 subscale and ≥ 6 full-symptom panic attacks during the 2 weeks before the screening visit. In the 2 weeks between screen and baseline, they had to experience ≥ 3 full-symptom panic attacks per week. - Patients had to have a Covi Anxiety Scale total score greater than their Raskin Depression Scale 58 total score at the baseline visit. - Women of child bearing potential had to have a negative serum pregnancy test result at screening, and sexually active women participating in the study had to use a medically acceptable form of contraception. - Patients who completed the 12-week open-label treatment phase were considered responders and therefore eligible for the double blind continuation phase if they had ≤ 1 full-symptom panic attack per week during the last 2 weeks of open-label treatment and a Clinical Global Impressions Improvement (CGI-I)57 score of 1 or 2 relative to their baseline score. **Exclusion criteria :** Patients were excluded if they had any clinically important medical condition that could compromise the study or be detrimental to the

	patient; any clinically significant current or predominant Axis I or II diagnosis other than panic disorder (with or without agoraphobia) within 6 months of study day 1; drug or alcohol dependence or abuse as defined in the DSM-IV within 1 year of study day 1; a history or presence of any psychotic illness, bipolar disorder, organic brain disease, clinically important head trauma, or seizure disorder; acute suicidality; positive urine drug screen for illicit drugs; cognitive behavioral therapy within 30 days preceding study day 1; introduction or change in intensity of formal psychotherapy within 60 days of study day 1; or a screening or baseline Montgomery-Asberg Depression Rating Scale (MADRS) 59 score ≥ 22. Patients were also excluded if they had used investigational drugs, investigational procedures, electroconvulsive therapy, antipsychotics, fluoxetine, or triptans within 30 days of study day 1; had used antidepressants (other than fluoxetine), monoamine oxidase inhibitors, lithium, sedative hypnotics other than zaleplon or zolpidem, stimulants, or any herbal or homeopathic products intended to treat anxiety, depression, or insomnia within 14 days of study day 1; or had used benzodiazepines or similar anxiolytics or non-psychopharmacologic drugs with psychotropic effects within 7 days of study day 1 (except non-psychopharmacologic drugs taken at a stable dose for at least 3 months before study day 1). Treatments that were prohibited during study participation included any treatment prohibited before study day 1.
Interventions	Venlafaxine ER vs placebo
Outcomes	Preventing relapse: - Relapse of panic disorder was defined as having ≥ 2 full-symptom un expected or situational panic attacks per week for 2 consecutive weeks or having been discontinued from the double-blind phase because of loss of effectiveness, as determined by the investigators. - The primary efficacy endpoint was the time to relapse for patients who entered the double-blind continuation phase of the study. A number of secondary measures were used to further evaluate efficacy, psychiatric disability, and improvement in quality of life. The secondary efficacy measures included (1) the percentage of patients having no full-symptom panic attacks in the previous 2-week period; (2) Panic Disorder Severity Scale (PDSS)0 total score; (3) the number of full-symptom panic attacks during the 2-week period: (4) CGI-S; (5) Phobia Scale (fear and avoidance): (6) anticipatory anxiety, and (7) the percentage of patients with Panic and Anticipatory Anxiety Scale (PAAS)" limited panic attack symptoms Safety, the incidence and severity of treatment-emergent adverse events.
Notes	**Funding:** This study was sponsored by Wyeth Research, Collegeville, Pa.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients eligible to participate in the double-blind continuation phase were randomly assigned to receive either venlafaxine ER or placebo
Allocation	Low risk	During the transition from the open-label to double-blind phase of the study, patients took the same number of capsules per

concealment (selection bias)		day of study medication as they had taken during the open-label phase of the study to preserve the blinding
Blinding of participants and personnel (performance bias)	High risk	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study. (Patients assigned to continuation treatment with placebo had their open-label dosage tapered down for 2 weeks or longer if medically indicated. Those assigned to treatment with venlafaxine ER continued to receive their open-label dosage for up to 6 months of double-blind treatment, followed by a poststudy taper off medication of 14 ±3 days)
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	High risk	Withdrawal form study : Before baseline phase: 8 Open label phase: 137 (44%) Double blind phase 90 (51%), venlafaxine 36, placebo 54.
Selective reporting (reporting bias)	High risk	withdrawal symptoms were not reported.
Other bias	Low risk	Comment: study appears to be free from other sources of bias

Georgotas 1989

Methods	**Design**: RCT Prerandomisation phases: - Acute phase = single-blind period of at least 7 days, Patients were administered placebo - Double-blind treatment phase: patients were randomly assigned to one of three double-blind treatment conditions: nortriptyline, phenelzine, or placebo for 7-9 weeks. - Continuation phase: The mean (± SD) length of this phase was 16.7±2.8 weeks. All patients in the continuation phase were treated with either nortriptyline or phenelzine. Duration post randomisation: Follow-up phase: 1-year maintenance phase. **Aim:** The present study was a placebo-controlled comparison of the efficacy of nortriptyline hydrochloride (TCA's) and phenelzine sulfate (MAOI) in preventing recurrences of major depression in elderly patients
Participants	**Country:** USA (New york university) **Setting:** outpatients This study was conducted at the Depression Studies Program of New York University, New York, an outpatient research facility for the study and treatment of affective disorders. **Type of AD:** Nortriptyline (TCA), Phenelzine (MAOIs). ***Duration of antidepressant treatment pre randomisation:** - only one week of placebo. - Double-blind treatment phase: nortriptyline, phenelzine, or placebo for 7-9 weeks.

	Patients given placebo who had not responded were crossed over to either nortriptyline or phenelzine under double-blind conditions. Responders to the first antidepressant after 7 to 9 weeks of treatment entered the continuation phase. - Continuation phase: patients were treated with nortriptyline or phenelzine. The mean (± SD) length of this phase was 16.7±2.8 weeks. After finishing this phase, about 50% of patients were switched, on a randomised, double-blind basis from their continuation medication to placebo. **Duration of antidepressant treatment post stabilisation:** **Follow-up phase**: 1-year maintenance phase. **Number of participants**: Fifty-one outpatients **Total number of randomised participants**: 51 (23 placebo, 13 nortriptyline hydrochloride, 15 phenelazine sulfate) **Primary diagnosis**: unipolar major depressive disorder as defined by **Research Diagnostic Criteria (RDC**) Severity of depressive symptoms at randomisation(mean, SD): Patients switched to placebo had significantly (F[l,22] =7,64; P=.01) more prior episodes of depression (mean±SD = 7.7±9.2) than did those maintained on phenelzine (mean±SD=1.0±1.6). Additionally, patients switched to placebo were statistically significanfcly more depressed before treatment (F[l,22] = 4.33; P<.05) by Hamilton score (mean±SD = 24.6±4.4) than were those patients who continued to receive phenelzine (mean±SD =21.3±3.4). -There were no significant differences in age, sex, length ofthe index episode, age of onset of the first depressive episode, number of prior episodes, pretreatment Hamilton score, Hamilton score after continuation treatment, and RDC subtype between patients taking nortriptyline and those switched from nortriptyline to placebo. **Comorbidity**: No **Gender distribution** (F/ M): NT (16/11), PE (12/12) **Mean age (year) (SD):** NT (65.6±6.4), PE (64.0±5.6) **Inclusion criteria**. Patients included in the study were 55 years of age and above and were independently diagnosed by two psychiatrists as suffering from unipolar major depressive disorder as defined by Research Diagnostic Criteria (RDC). A score of 16 or greater on the 21-item Hamilton Rating Scale for Depression was also required for inclusion. **Exclusion criteria** Patients were excluded if they showed evidence of moderate to severe dementia as evidenced by a score on the Global Deterioration Scale of 4 or more, drug or alcohol dependence, a serious neurologic disorder, or other preexisting major psychiatric disorders. Patients who entered the acute phase were administered placebo during a single-blind period of at least 7 days. Patients who still met the entry criteria after this were randomly assigned to one of three double-blind treatment conditions: nortriptyline, phenelzine, or placebo. After 7 weeks of treatment, patients given placebo who had not

	responded were crossed over to either nortriptyline or phenelzine under double-blind conditions (The criteria for a response to treatment was a Hamilton score less than or equal to 10). Responders to the first antidepressant after 7 to 9 weeks of treatment entered the continuation phase. Patients had to be free from illness for at least 4 months and had to sustain Hamilton scores less than or equal to 10 for at least 2 consecutive months before leaving this phase and entering the next phase. All patients in the continuation phase were treated with either nortriptyline or phenelzine. After finishing the continuation phase, about 50% of patients were switched, on a randomised, double-blind basis from their continuation medication to placebo. Patients were then followed for a year.
Interventions	Nortriptyline hydrochlorlde group (N:13), Phenelzine sulfate group (N:15) vs Placebo group (N: 23)
Outcomes	A recurrence was defined if a patient met RDC (Research Diagnostic Criteria) for definite major depression and had a Hamilton score equal to or greater than 16 during the year of follow-up. criterion for clinical response was a Hamilton score less than or equal to 10,
Notes	This study was conducted at the Depression Studies Program of New York University.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	Unclear risk	Not reported
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Low risk	Comment: study appears to be free from other sources of bias

Gorwood 2007

Methods	**Design:** RCT **Prerandomisation phases**: 12-week open-label treatment period **Duration post randomisation**: 24-week, **Aim**:The present study investigated the efficacy and tolerability of escitalopram in the prevention of relapse of major depressive disorder

	(MDD) in older patients who had responded to acute treatment with escitalopram.
Participants	**Country**: seven European countries **Setting**: outpatients (private or hospital outpatient clinics) **Type of AD**: escitalopram (selectieve serotonine-heropnameremmers of SSRI's) */ **Duration of antidepressant treatment prerandomisation**: This study started with a 12-week open-label treatment period. During this period, patients received 10 mg escitalopram per day during the first week and the dose could be increased to 20 mg per day at week 2 based on the clinical judgment of the investigator. The dose could subsequently be reduced to 10 mg per day in case of poor tolerability. From week 6, no dose adjustment was allowed. Patients who were in remission were eligible for randomization. **Duration of antidepressant treatment post stabilisation**: 24-week. **Number of participants**: 405 patients. **Total number of randomised participants**: 305 patients, (152 escitalopram,153 placebo). **Primary diagnosis**: older patients with Major Depressive Disorder (MDD) **Severity of depressive symptoms at randomisation(mean, SD**): - Patients who were in remission [MADRS] total score ≤12 by the end of the 12-week open-label period were eligible for randomisation to either escitalopram or placebo. - There were no clinically relevant differences in the severity of depression as measured by MADRS or CGI-S between patients treated with escitalopram or placebo at the start of the double-blind period. Patients randomised to double-blind treatment had mean MADRS total scores of 5,3 (both treatment groups) at week 12. **Comorbidity**: No **Gender distribution F**: escitalopram 119 (78%), placebo 121(79%) **Mean age (year) (SD):** The average age was 73 ± 5.4 years, escitalopram 73 (64-86), placebo 72 (65-90) **Deinition of remission**: Patients were in remission if Montgomery-Åsberg Depression Rating Scale [MADRS] total score ≤12. **Inclusion criteria:** Patients aged ≥65 years were eligible if they had a MADRS total score ≥22, duration of the current major depressive episode (MDE) of at least 4 weeks, and a Mini-Mental State Examination total score ≥24 at the screening visit. The patients should have no un stabilized serious illnesses on the basis of medical history and the screening results of a physical examination, electrocardiogram, and clinical laboratory tests. **Exclusion criteria:** Patients with any of the following disorders were excluded: 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 resulting from a general medical condition as defined in DSM-IV-TR; and Any substance abuse disorder, presence or history of a clinically significant neurologic disorder, neurodegenerative disorder, and any personality disorder that might compromise the study. Patients were also excluded if they were at risk of suicide according to the

	investigator or had a rating ≥5 points on item 10 “suicidal thoughts” of the MADRS or had made a suicide attempt within the past year. Patients were also excluded if they had used any of the following recent/concomitant therapies: oral antipsychotic drugs within 2 months and depot preparations within 6 months before screening; or electroconvulsive therapy or lithium, carbamazepine, valproate, or valpromide within the past month before screening. Disallowed drugs within the last week before screening were: antidepressants (five weeks for fluoxetine); any benzodiazepines (except benzodiazepines in patients under stable low dose for at least six months); any nonbenzodiazepine anxiolytics or hypnotics (other than zolpidem, zopiclone, or zaleplon); serotonin agonists (for example, triptans); and any drug with potential psychotropic effects. In addition, patients with a history of severe drug allergy or hypersensitivity, or known hypersensitivity to citalopram and/or escitalopram, patients who continued or began formal psychotherapy, patients with current depressive symptoms that had been resistant to two well-conducted antidepressant treatments, and patients who had demonstrated a lack of response to previous treatment with citalopram or escitalopram (including current episode) were excluded.
Interventions	Escitalopram vs placebo
Outcomes	**Primary outcome:** Relapse: - The primary efficacy parameter was the time to relapse, defined as either an increase in MADRS total score to 22 or more or lack of efficacy as judged by the investigator. **Relapse.** - The primary efficacy analysis used a two-tailed log-rank test to compare the time to relapse for patients treated with escitalopram versus placebo using SAS version 9.1 as statistical software. In addition, Kaplan-Meier survival curves were produced and the Cox proportional hazards model for survival data were used to estimate hazard ratios. A $\chi 2$ test was used to compare the crude proportions of relapsed patients. - The prospectively defined secondary efficacy parameters included change in scores for the MADRS, CGI-S, and CGI-I, MADRS remitters (MADRS ≤12), MADRS responders (≥50% reduction in MADRS total score), CGI-S remitters (CGI-S ≤2), and CGI-I responders (CGI-I ≤2). - The secondary analysis of time to relapse, was based on the Cox proportional hazard model. **Remission:** - Patients were in remission if [MADRS] total score ≤12 by the end of the 12-week open-label period. Secondary outcome: Tolerability, overall withdrawal rate, incidence of AEs - The tolerability and safety evaluations were based on spontaneously reported adverse events (AEs), vital signs, body weight, and physical examination. Discontinuation symptoms were assessed by evaluation of AEs during the one-week taper period (tapering of escitalopram for patients randomised to the placebo arm) and during the one-week taper period for patients who completed the study.
Notes	**Funding:** Philip Gorwood and Cornelius Katona have received honoraria from and have conducted clinical research supported by H. Lundbeck A/S.

	Emmanuelle Weiller and Ole Lemming are full-time employees of H. Lundbeck A/S

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	After the open-label period, eligible patients were assigned to escitalopram or placebo treatment according to a computer-generated randomisation list drawn up by H. Lundbeck A/S
Allocation concealment (selection bias)	Low risk	Study medications were tablets for oral administration of identical appearance, taste, and smell. The details of the randomisation series were unknown to any of the investigators and were contained in a set of sealed opaque envelopes.
Blinding of participants and personnel (performance bias)	Low risk	All study personnel and participants were blinded to treatment assignment for the duration of the study.
Blinding of outcome assessment (detection bias)	Low risk	All study personnel were blinded to treatment assignment for the duration of the study
Incomplete outcome data (attrition bias)	High risk	The overall withdrawal rate: Open period: 72 Bubble blind period: 63 (placebo) And 23 (Escitalopram)
Selective reporting (reporting bias)	High risk	No discontinuation symptoms mentioned.
Other bias	Low risk	Comment: study appears to be free from other sources of bias

Harrison 1986

Methods	**Design:** RCT. **Prerandomisation phases**: **Duration of Treatment at T2 in phenelzine group** = 16.4 weeks, in placebo Group = 20,1 **T2=**point of randomisation to continuation treatment with phenelzine or placebo. **Duration post randomisation:** Follow up= 6 months **Aim:** The aim of this study to demonstrate the efficacy of continuation therapy with phenelzine in maintaining clinical response after acute treatment.
Participants	**Country**: USA **Setting**: outpatients attending a university-affiliated depression research clinic **Type of AD**: Phenelzine =monoamine oxidase inhibitor (MAOI) **Duration of antidepressant treatment pre randomisation:** **Duration of Treatment at T2 in phenelzine group** = 16.4 weeks

	Duration of Treatment at T2 in placebo Group = 20,1. T2=point of randomisation to continuation treatment with phenelzine or placebo. **Duration of antidepressant treatment post stabilisation**: 6 months **Number of participants:** 12 patients. **Total number of randomised participants**: 12 patients, (Phenelzine 5, Placebo 7) **Primary diagnosis**: Dysthymic disorder with long histories of depressive disorder (mean duration=15 years) **Severity of depressive symptoms at randomisation(mean, SD):** There were no significant differences in HAM-D and CGI scores between groups at the point of randomisation to continuation therapy on the HAM-D (t= 1.5) or the CGI (t=1.2). **Comorbidity:** No **Gender distribution F:** 83% of all participants were women **Mean age (year) (SD):** Most patients were in their thirties or forties and had long histories of depressive disorder. Deinition of remission: The criterion for response was a score of 1 or 2 (i.e., “very much improved” or “much improved”) on the degree of improvement measure of the Clinical Global Impressions (CGI) scale. **Inclusion criteria:** All patients met DSM-III criteria for dysthymic disorder, which includes illness duration of at least 2 years as an essential criterion for adults. To be eligible for entrance into the study, patients had to have shown a significant antidepressant response to phenelzine. **Exclusion criteria** Patients were not eligible if they had been treated with an adequate dose of antidepressant medication (defined as the equivalent of more than 150 mg of imipramine daily for at least 2 weeks) during the current depressive episode or if they were not considered sufficiently reliable to comply with strict research requirements, including dietary restrictions.
Interventions	Phenelzine Group (N=5) vs Placebo Group (N=7)
Outcomes	**Relaps:** Patients were considered to have relapsed and were withdrawn from the protocol if they scored 3 or more on the CGI for 2 consecutive weeks. Paired t tests were used to compare item responses over time by treatment group for the SCL-90, IGLF, and HAM-D. The proportions of relapses in the active drug and placebo groups were compared by means of chisquare tests. AU tests were two-tailed. Relapse was manifested by a return of both anxious and depressive symptoms and also a decline in the subjective sense of well-being and overall social functioning. The criterion for response was a score of 1 or 2 (i.e., “very much improved” or “much improved”) on the degree of improvement measure of the Clinical Global Impressions (CGI) scale. Side Effects: side effects were rated with a side-effects rating scale.
Notes	Funding: not reported Small sample size (12 patients), larger samples clearly are needed.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	The double-blind condition was maintained by providing individual daily medication packets in which the number of tablets was kept constant by substituting matching placebo.
Blinding of participants and personnel (performance bias)	Unclear risk	Not reported
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Low risk	2 patients withdrew from the study
Selective reporting (reporting bias)	Low risk	Mood worsening rather than physical complaint was the predominant symptom of withdrawal.
Other bias	Unclear risk	Not reported

Hochstrasser 2001

Methods	**Design:** RCT **Prerandomisation phases:** **Period I**: 6-9 weeks of open, acute treatment with citalopram . **Period II:** 16 weeks of open continuation treatment with citalopram to consolidate remission **Duration post randomisation**: Period III: minimum of 48 weeks of double-blind maintenance treatment with citalopram or placebo. The lengths of prophylactic maintenance treatment were between 48 and 77 weeks. **Aim:** Comparison of prophylactic efficacy of citalopram versus placebo in unipolar, recurrent depression. tudy ID: Prophylactic effect of citalopram in unipolar, recurrent depression: placebo-controlled study of maintenance therapy.
Participants	**Country:** nine European countries (Austria, Belgium, Finland, France, Italy, The Netherlands, Norway, Switzerland and the UK). **Setting:** Patients were in- and out-patients recruited from 54 centers (psychiatric institutions and, in the UK, general practitioner research settings) **Type of AD**: citalopram (selectieve serotonine-heropnameremmers of SSRI's) **Duration of antidepressant treatment pre randomisation**:

	Period I: 6-9 weeks of open, acute treatment with citalopram . **Period II:** 16 weeks of open continuation treatment with citalopram to **consolidate remission** **Duration of antidepressant treatment post stabilisation**: 48-week. **Number of participants**: 427 patients **Total number of randomised participants**: 264 patients (132 on citalopram; 132 on placebo). **Primary diagnosis:** unipolar, recurrent depression. **Severity of depressive symptoms at randomisation(mean, SD):** - There were no differences in CGI score distribution: about one-third of patients in both groups were rated as moderately ill and the rest as markedly ill or above. - All patients completing Period II with a MADRS score ≤11 were randomised. - The average entry MADRS score into Period III was 4.2 (s.d.-3.4) in the citalopram group and 4.3 (s.d.-3.4) in the placebo group. **Comorbidity:** In both groups, the medical conditions most frequently reported were hypertension, menopausal/climacteric states, arthrosis, dorsalgia, asthma, various allergies, migraine and other headaches. **Gender ratio (male/female**): citalopram 43/89, placebo 33/99 **Mean age (year) (SD**): citalopram 43.8+97, placebo 42.4±11,5 **Deinition of remission**: No **Inclusion criteria:** 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; Reference Montgomery and ÅsbergMontgomery & Åsberg, 1979) and 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.
Interventions	Citalopram (132p) vs Placebo (132p)
Outcomes	The prophylactic efficacy of citalopram in recurrent depression: - The time from randomisation to recurrence of a new depressive episode. - Recurrence was defined as a MADRS total score ≥22, confirmed after 3-7 days. - Potential contributing factors: Analysis of the potential influence of clinically relevant covariate (MADRS score at entry into Period I, age and treatment by a general practitioner) on the risk of recurrence, and association between a positive family history of depression and risk for recurrence. - Secondary outcome measures were MADRS and CGI score development. Safety and tolerability - The most frequent adverse events

	- The number of premature discontinuation owing to adverse events during prophylactic treatment. - Serious adverse event - Changes in laboratory or vital sign parameters - Discontinuation symptoms.
Notes	Declaration of interest: Funded by H. Lundbeck A/S.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation was done on a 1:1 basis, irrespective of citalopram dose and without any stratification procedure.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	Unclear risk	Not reported
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	High risk	Withdrawal form study: Period I: 100 patients Period II: 58 patients Prior to unblinding of the treatment code, 5 patients
Selective reporting (reporting bias)	Low risk	potential discontinuation symptoms: dizziness, headache, nausea and vertigo in the first few weeks following randomisation
Other bias	Low risk	Comment: study appears to be free from other sources of bias

Lustman 2006

Methods	**Design:** RCT **Prerandomisation phases:** phase 1 (induction)= 16 weeks of open-label treatment. **Duration post randomisation**: phase 2 (maintenance) = 52 weeks or until depression recurred **Aim:** The aim of our study was to determine whether maintenance treatment with sertraline hydrochloride prevents recurrence of comorbid depression in diabetes and influences the longer-term course of glycemic control. tudy ID: Sertraline for Prevention of Depression Recurrence in Diabetes Mellitus A Randomized, Double-blind, Placebo-Controlled Trial. **Total study duration**: 6 years **Duration of treatment period**: 16+52 weeks **study ID**: Sertraline for Prevention of Depression Recurrence in Diabetes Mellitus A Randomized, Double-blind, Placebo-Controlled Trial.

Participants	**Country:** USA **Setting**: Outpatient clinics at Washington University, St Louis, Mo, the University of Washington, Seattle, and the University of Arizona, Tucson **Type of AD**: sertraline hydrochloride (selectieve serotonine-heropnameremmers of SSRI's) **Duration of antidepressant treatment pre randomisation**: The study was a 2-phase depression treatment trial. In phase 1 (induction), patients with major depressive disorder received up to 16 weeks of open-label treatment with sertraline. **Duration of antidepressant treatment post stabilisation**: In phase 2 (maintenance), those who achieved recovery from depression were randomised to either sertraline or placebo and were followed for up to 52 weeks or until depression recurred. **Number of participants**: 351 patients. **Total number of randomised participants**: 152 patients, (79 sertraline,73 placebo). **Primary diagnosis**: major depressive disorder as defined in DSM-IV in patients with diabetes type 1 or type 2. */ **Severity of depressive symptoms at randomisation(mean, SD):** BDI score at randomisation mean ± SD: sertraline (4,4±3,0), placebo (3,5 ±2,6) HDRS score at randomisation mean ± SD: sertraline (3,3±2,7), placebo (4,0 ± 3,5) HBA1c level at randomisation, mean ± SD,%: sertraline (7,9 ±1,6) , placebo (7,8 ±1,6) **Comorbidity**: dibetes type 1 or 2 **Gender distribution** F: sertraline 46 (58.2), placebo 121(79%) **Mean age (year) (SD**): The average age was 52.8 ± 12.3 years, sertraline 50.5±11.7 placebo 55.3±12.5 **Deinition of remission**: Recovery from depression was defined per DSM-IV criteria as a period of at least 2 months during which there were no significant symptoms of depression, which was defined operationally as 4 consecutive twice-monthly BDI scores of 9 or less within 4 months of beginning sertraline treatment and subsequent confirmation of the absence of major depression by diagnostic reevaluation **Inclusion criteria**: To enter the induction phase, patients were required to be 18 to 80 years of age, have type 1 or type 2 diabetes and major depressive disorder as defined in DSM-IV, and have a total score of 14 or greater on the Beck Depression Inventory (BDI) or 15 or greater on the Hamilton Depression Rating Scale (HDRS). **Exclusion criteria:** Patients excluded from participation were those with active suicidal or homicidal ideation, a history of attempted suicide, current alcohol or other substance abuse disorders, a history of bipolar depression or any psychotic disorder, or a medical contraindication to sertraline treatment. Outpatient clinics at Washington University, St Louis, Mo, the University of Washington, Seattle, and the University of Arizona, Tucson.
Interventions	Sertraline continued at recovery dose or identical-appearing placebo.
Outcomes	The primary outcome was length of time (measured as the number of days after randomisation) to recurrence of major depression as defined in DSM-IV.

	- The Kaplan-Meier method was used to estimate the survivor functions, and the nonparametric log-rank test was used to test the principal study hypothesis that the recurrence-free interval was significantly longer in patients receiving sertraline than in those receiving placebo. - Mean Beck Depression Inventory (BDI) score at time points during induction and maintenance phases of the study. The recurrence BDI score was calculated for the subset of patients who had a recurrence of major depression during the maintenance phase. -The Cox proportional hazards regression model was used to calculate the overall effect of treatment in light of baseline differences between treatment groups, and it was also used in secondary analyses to determine whether factors other than treatment effect were responsible for depression recurrence. The secondary outcome was glycemic control, which was assessed via serial determinations of glycosylated hemoglobin levels. - Glycosylated hemoglobin (HbA1c) levels at baseline, randomisation, and during the depression-free interval leading up to recurrence (includes all of the post randomization HbA1c levels). Medication adverse effects.
Notes	Funding/Support: This study was supported in part by grants DK36452, DK53060, and DK59364 from the National Institutes of Health, Bethesda, Md, and an unrestricted educational grant from Pfizer, Inc, New York, NY. Role of the Sponsor: The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.*/ This study clearly shows the advantage of sertraline over placebo in preventing recurrence of depression in patients with diabetes.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised using a computer-generated algorithm.
Allocation concealment (selection bias)	Low risk	Administration of treatment and all of the study evaluations were performed by personnel not involved in any aspect of the randomisation process. Only the data managers, study statisticians, and the data monitoring committee saw unblinded data, but none of them had any contact with study participants. Blinded tapering was accomplished by dovetailing the induction- and maintenance-phase medication. All of the clinician-based assessments, including the DISH scale and HDRS evaluations, were performed by individuals blinded to treatment assignment. sertraline and placebo have identical-appearing.
Blinding of participants and personnel (performance bias)	Low risk	All of the clinician-based assessments, including the DISH scale and HDRS evaluations, were performed by individuals blinded to treatment assignment.??

Blinding of outcome assessment (detection bias)	Low risk	Administration of treatment and all of the study evaluations were performed by personnel not involved in any aspect of the randomisation process. Only the data managers, study statisticians, and the data monitoring committee saw unblinded data, but none of them had any contact with study participants. Blinded tapering was accomplished by dovetailing the induction- and maintenance-phase medication.
Incomplete outcome data (attrition bias)	High risk	The overall withdrawal rate: - induction phase: 195 patients. - 4 patients refused to continue after induction phase. - maintenance phase: 22 patients
Selective reporting (reporting bias)	High risk	No discontinuation symptoms mentioned
Other bias	Unclear risk	Not reported

Lyketsos 2011

Methods	**Design:** RCT **Prerandomisation phases**: 12-week open-label treatment period **Duration post randomisation**: 24-week, **Aim**: The primary aim was to compare the effect of escitalopram in preventing relapse of MDD among young-old and old-old patients. A secondary objective was to compare the initial response to open-label escitalopram in these two age groups. **study ID**: Are old-old patients with major depression more likely to relapse than young-old patients during continuation treatment with escitalopram?
Participants	**Country**: seven European countries. **Setting**: outpatients with MDD. **Type of AD**: escitalopram (selectieve serotonine-heropnameremmers of SSRI's) **Duration of antidepressant treatment prerandomisation**: - open-label treatment: 12-weeks During this period, outpatients aged at least 65 years received escitalopram 10mg/day during the first week; the dose could be increased to 20mg/day at Week 2, based on the clinical judgement of the investigator. Subsequently the dose remained constant for the remaining open label period. At the end of the 12-week open-label period, patients who achieved remission, were eligible for randomization to either continue escitalopram or to switch to placebo in a 1:1 ratio. **Duration of antidepressant treatment post stabilisation:** 24-week. **Number of participants**: 405 patients. Patients aged 65-74 yearsa (n = 254) Patients aged ≥75 years (n = 151) **Total number of randomised participants**: - Of the 254 young-old patients entering open-label treatment, 215 achieved remission (78%) and 197 were randomly assigned to treatment with escitalopram (n = 102) or placebo (n = 95). - Of the 151 old-old patients entering the open-label period, 118 achieved remission (72%) and 108 were randomly assigned to treatment with escitalopram (n = 50) or placebo (n = 58) - A total of 305 patients entered double-blind treatment (153 placebo, 152

	escitalopram) **Primary diagnosis**: young-old patients (78%) and old-old patients (72%) with Major Depressive Disorder (MDD) **Severity of depressive symptoms at randomisation(mean, SD):** - At the end of the 12-week open-label period, patients who achieved remission, defined by a Montgomery Åsberg Depression Rating Scale (MADRS) score ≤12, were eligible for randomisation to either continue escitalopram, or to switch to placebo in a 1:1 ratio. - There were no clinically relevant differences in the severity of depression as measured by MADRS or CGI-S between young-old and old-old patients. - Old-old patients randomised to double-blind treatment had mean MADRS total scores of 5.8 (both treatment groups) at week 12, compared to 5.0 for young-old patients. **Comorbidity:** Hypertension, Myocardial ischemia? Localised osteoarthritis, Osteoarthritis, Hypercholesterolaemia, Insomnia, Osteoporosis, Diabetes mellitus, Diabetes mellitus, non-insulin-dependent, Varicose vein, Coronary artery disease, Gastritis, Cardiac failure, Cataract, Back pain, Hypothyroidism. **Gender distribution F**: women: 193 (76%) in patients aged 65-74 years group. 120 (79%) in Patients aged ≥75 years group. **Mean age (year) (SD):** Patients were aged ≥75 years (old-old) or 65-74 years of age (young-old) **Deinition of remission**: Patients were in remission if Montgomery-Åsberg Depression Rating Scale [MADRS] total score ≤12. Complete remission (MADRS ≤5) was defined post hoc. **Inclusion criteria**: Inclusion and exclusion criteria are described in detail by Gorwood et al. Patients were required to have a MADRS score ≥22 and an MMSE score ≥24 at entry. **Exclusion criteria**: Inclusion and exclusion criteria are described in detail by Gorwood et al. Patients with severe or unstable medical co-morbid diseases were excluded. Patients eligible for study were outpatients with a primary diagnosis of MDD (assessed by psychiatrists using the Mini International Neuropsychiatric Interview), moderate or severe, according to DSM-IV-TR criteria [17], and who gave informed consent.
Interventions	escitalopram group: 152p (young-old patients: 102p, old-old patients: 50p) vs Placebo group:153p (young-old patients :95p, old-old patients: 58p).
Outcomes	**Relapse** - Time to relapse based on the Cox model (proportional hazards regression) , the effect of age - Relapse was defined either as a MADRS total score ≥22 at a single visit, or an unsatisfactory treatment effect (lack of efficacy), as judged by the local **investigator.** - This definition was extended in a sensitivity analysis to include patients who met the DSM-IV criteria for MDE or who attempted suicide. **Tolerability** The tolerability and safety evaluations were based on spontaneously

	reported adverse events (AEs), vital signs, body weight, and physical examination. **Efficacy:** - Efficacy was assessed using the Montgomery Åsberg Depression Rating Scale (MADRS). - All efficacy analyses in the double-blind period were conducted on the modified intent-to-treat (ITT) dataset, consisting of all randomised patients who took at least one dose of trial medication in the double-blind treatment period, using the last observation carried forward (LOCF) approach to impute missing data. Comparisons between age groups during the open-label period were performed using analysis of covariance (ANCOVA) with age group and country as factors, and with the score at randomisation as a covariate.
Notes	**Funding:** The original randomised controlled trial was sponsored by H. Lundbeck A/S. **Conflect:** CK has received honoraria from, and have conducted clinical research supported by H. Lundbeck A/S. PG is employed by University Paris Descartes and has received grants from Eli Lilly and Servier, honoraria from Bristol-Myers Squibb, Eli Lilly, Lundbeck, Servier and UCB-Pharma, and participated in advisory boards for Janssen, Lundbeck, Servier and Wyeth. CGL has received grant support (research or CME) from NIMH, NIA, Associated Jewish Federation of Baltimore, Weinberg Foundation, Forest, Glaxo-Smith-Kline, Eisai, Pfizer, Astra-Zeneca, Lilly, Ortho-McNeil, Bristol-Myers, Novartis. He is a consultant/advisor to Astra-Zeneca, Glaxo-Smith Kline, Eisai, Novartis, Forest, Supernus, Adlyfe, Takeda, Wyeth, Lundbeck, Merz, Lilly, Genentech, Pfizer, and has received honoraria or travel support from Pfizer, Forest, Glaxo-Smith Kline, Health Monitor. EW is a fulltime employee of H. Lundbeck A/S.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	After the open-label period, eligible patients were assigned to escitalopram or placebo according to a computer-generated randomization list drawn up by H. Lundbeck A/S.
Allocation concealment (selection bias)	Low risk	Study medications were tablets for oral administration of identical appearance, taste and smell
Blinding of participants and personnel (performance bias)	Low risk	All study personnel and participants were blinded to treatment assignment for the duration of the study.
Blinding of outcome assessment (detection bias)	Low risk	Details of the randomization were unknown to any of the investigators and were contained in a set of sealed opaque envelopes.
Incomplete outcome data (attrition bias)	High risk	The overall withdrawal rate: -Open period: young-old patients (15.4%) For old-old patients (21.9%) -Bubble blind period:

		Escitalopram group 5.9% of young-old and 8.0% for old-old patients. Placebo group: 9.5% for young-old patients and 6.9% for old- old patients
Selective reporting (reporting bias)	High risk	No discontinuation symptoms mentioned
Other bias	Unclear risk	Not reported

McGrath 2006

Methods	**Design:** RCT **Prerandomisation phases**: 1-week medication-free washout period 12-week course of open-label treatment with fluoxetine. **Duration post randomisation**: 52 week discontinuation phase (Fluoxetine or placebo), the first 6 months of this period were considered the continuation phase, and the remainder, the maintenance phase. **Aim**: This study was designed to test the predictive value of response pattern prospectively and to examine the data for other predictors of relapse. **study ID**: Predictors of Relapse in a Prospective Study of Fluoxetine Treatment of Major Depression
Participants	**Country:** USA **Setting:** A total of 627 patients 18 to 65 years of age who met DSM-IV criteria for a current episode of major depressive disorder were recruited by research programs at the New York State Psychiatric institute in New York City and the Depression Clinical and Re-search Program of Massachusetts General Hospital in Boston. **Type of AD**: fluoxetine (selectieve serotonine-heropnameremmers of SSRI's) **Duration of antidepressant treatment pre randomisation**: 1-week medication-free washout period 12-week course of open-label treatment with fluoxetine. **Duration of antidepressant treatment post stabilisation**: 52-week. **Number of participants**: 627 participants. **Total number of randomised participants**: 262 participants, Fluoxetine (131) vs Placebo (131) **Primary diagnosis:** Major Depressive Disorder (MDD) **Severity of depressive symptoms at randomisation(mean, SD):** HAM-D score was 4.9 (SD=3.1) at randomisation. **Comorbidity:** About two-thirds (35%) of the participants had one or more comorbid axis I disorder, most commonly panic disorder (13.3%), social phobia (12.4%), and alcohol dependence (10.6%) **Gender distribution F**: 55.3% were female **Mean age (year) (SD)**: a mean age of 38.2 years (SD=10.9), 18.3% of them were married, **Deinition of remission**: Treatment response was rated on the17-item Hamilton Depression Rating Scale (HAM-D) (22) and the Clinical Global Impression Scale (CGI) (23). HAM-D score was 4.9 (SD=3.1) **Inclusion criteria**:

	1- Medication-free washout period patients 18 to 65 years of age who met DSM-IV criteria for a current episode of major depressive disorder. No minimum score for severity of depressive symptoms was required for inclusion in the study. 2- Open phase: The mean HAM-D score at baseline was 17.7 (SD=4.1). 3- RCT phase: HAM-D score was 4.9 (SD=3.1) at randomization. **Exclusion criteria:** significant risk of suicide, pregnant, breast-feeding; were women not using effective contraception, unstable physical disorder, lifetime history of any organic mental disorder, psychotic disorder, or mania, history of seizures, 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 SSRI (defined as a 4-week trial of at least 40 mg of fluoxetine or the equivalent daily).
Interventions	Fluoxetine (131) vs Placebo (131).
Outcomes	The predictive value of response pattern for relapse prospectively. A “true drug” response pattern was defined as a delayed and persistent response to treatment, with the first CGI improvement score of 2 or less occurring after the second week of treatment. A “placebo” response pattern was defined as an early and/or nonpersistent response, Relapse was defined as having at least 2 consecutive weeks of ratings of less than “much improved” on the CGI improvement scale compared with ratings at entry into the study. Relapse during the double-blind discontinuation phase was de-fined as having at least 2 consecutive weeks of ratings of less than“much improved” on the CGI improvement scale compared withratings at entry into the study. The inferences are based on a model for the hazard as a functionof treatment (fluoxetine or placebo), response pattern group (“truedrug” response or “placebo” response), the interaction betweentreatment and response pattern group, and eight covariates: age,gender, neurovegetative symptom pattern (positive or negative),chronicity (as measured on the 6-point scale), subtype of major de-pression (atypical, melancholic, or neither), HAM-D score beforethe washout period, HAM-D score at randomization, and study site(New York City or Boston) Chronicity was originally measured on a 6-point scale.
Notes	**Funding:** Supported in part by NIMH grant R10-MH56058 to Dr. McGrath and infrastructure and salary support from the State of New York. Medication donated by Eli Lilly. Potential conflicts of interest: Dr. McGrath has provided scientific consultation or served on advi-sory boards for GlaxoSmithKline and Somerset Pharmaceutic als. He has received research grant support from Eli Lilly, GlaxoSmithKline,Lipha, and Organon Pharmaceutic als. Dr. Stewart has been on the speakers bureau

	of, been a consultant to, or received research sup-port from Eli Lilly, Forest, GlaxoSmithKline, Organon, Shire, and Som-erset Pharmaceuticals. Dr. Quitkin provided scientific consultation served on advisory boards for Eli Lilly, Organon, and Pfizer and heldshares of Cyberonics stock. Dr. Alpert has received research supportfrom Abbott Laboratories, Alkermes, Lichtwer Pharma GmbH, LorexPharmaceuticals, Aspect Medical Systems, AstraZeneca, Bristol-MyersSquibb, Cephalon, Eli Lilly, Forest Pharmaceuticals, GlaxoSmithKline,Johnson & Johnson Pharmaceuticals, Novartis, Organon, PamLab,Pfizer, Pharmavite, Roche, Sanofi/Synthelabo, Solvay Pharmaceuti-cals, and Wyeth-Ayerst Laboratories. He has received honoraria from Eli Lilly and Organon and has advisory or consultative relationships with Pamlab and Pharmavite. Dr. Nierenberg has provided scientific consultation for Bristol-Myers Squibb, Janssen Pharmaceutica, EliLilly, Genaissance, GlaxoSmithKline, Innapharma, Neuronetics,Pfizer, Sepracor, and Shire and has received research support fromBristol-Myers Squibb, Cederroth, Cyberonics, Eli Lilly, Forest Pharma-ceuticals, GlaxoSmithKline, Janssen Pharmaceutica, LichtwerPharma, National Alliance for Research on Schizophrenia and De-pression, NIMH, Organon, Pfizer, Stanley Foundation, and Wyeth-Ay-erst Laboratories. Dr. Nierenberg has also received honoraria fromCyberonics, Eli Lilly, GlaxoSmithKline, and Wyeth-Ayerst Laboratories.Dr. Fava has received research support from Abbott Laboratories,Lichtwer Pharma GmbH, and Lorex Pharmaceuticals. He has re-ceived speaking honoraria from Bayer AG, BioVail, Compellis, Cy-press Pharmaceuticals, Dov Pharmaceuticals, Grunenthal GmbH,Janssen Pharmaceutica, Knoll Pharmaceutical Company, Lundbeck,Sepracor, and Somerset Pharmaceuticals. In addition, Dr. Fava hasreceived research support and honoraria from Aspect Medical Sys-tems, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, Forest Pharmaceuticals, GlaxoSmithKline, Johnson & Johnson Pharmaceuti-cals, Novartis, Organon, Pharmavite, Pfizer, Roche, Sanofi/Syn-thelabo, Solvay Pharmaceuticals, and Wyeth-Ayerst Laboratories.Drs. Chen, Cheng, and Petkova report no competing interests

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	discontinuation phase during which they underwent random assignment under double-blind conditions with computer-generated randomisation, either to continue taking fluoxetine at the dose to which they had responded or to take placebo.
Allocation concealment (selection bias)	Low risk	Identical fluoxetine or placebo capsules were dispensed by a clinical research pharmacist who was blind to pattern of response
Blinding of participants and personnel (performance bias)	Low risk	a clinical research pharmacist who was blind to pattern of response
Blinding of outcome	Unclear risk	Not reported

assessment (detection bias)		
Incomplete outcome data (attrition bias)	High risk	withdrawal from the study: washout period: 57 open-label phase: 204 RCT: 115
Selective reporting (reporting bias)	High risk	withdrawal symptoms were not reported
Other bias	Low risk	Comment: study appears to be free from other sources of bias

Montgomery 2005

Methods	**Design:** RCT **Prerandomisation phases**: -12 weeks of open-label treatment with flexible doses (10-20 mg/day) of escitalopram. **Duration post randomisation**: -24 weeks of double-blind treatment with escitalopram or placebo. **Aim**:The aim of the present placebo-controlled study was to assess the effect of escitalopram in the treatment of patients with generalized SAD. **Study ID**: A 24-week randomised, double-blind, placebo-controlled study of escitalopram for the prevention of generalized social anxiety disorder **Method:** A total of 517 patients with a primary diagnosis of generalized SAD (per DSM-IV criteria) and a Liebowitz Social Anxiety Scale (LSAS) total score of > or = 70 received 12 weeks of open-label treatment with flexible doses (10-20 mg/day) of escitalopram. Of these patients, 371 responded (Clinical Global Impressions-Improvement scale [CGI-I] score of 1 or 2) and were randomly assigned to 24 weeks of double-blind treatment with escitalopram (10 or 20 mg/day) (N = 190) or placebo (N = 181)
Participants	**Country:** 11 countries in Europe, Canada, and South Africa **Setting**: outpatients **Type of AD**: escitalopram (selectieve serotonine-heropnameremmers of SSRI's) **Duration of antidepressant treatment prerandomisation**: 12 weeks of open-label treatment with flexible doses (10-20 mg/day) of escitalopram. **Duration of antidepressant treatment poststabilsation:** 24-week. **Number of participants**: 517 patients. **Total number of randomised participants**: 372 patients, (191 escitalopram,181 placebo). **Primary diagnosis**: moderate to severe generalized social anxiety disorder (SAD) (per DSM-IV criteria) and a Liebowitz Social Anxiety Scale (LSAS) total score of > or = 70. **Severity of depressive symptoms at randomisation(mean, SD):** - LSAS score: escitalopam (44.3 ± 20.8), placebo (43.2 ± 19.9). - CGI-S score: escitalopram (2.7 ± 1.0), placebo (2.6 ± 1.0) - MADRS total score: escitalopram (3.2 ± 3.1), placebo (3.3 ± 3.5). - SDS score Work: escitalopram (3.0 ± 1.9), placebo (2.8 ± 2.1). Social life: escitalopram (2.8 ± 1.9), placebo (2.9 ± 2.0).

	Family life: escitalopram (2.0 ± 1.9), placebo (2.0 ± 1.9). Comorbidity: No **Gender distribution**:(men) 53 % (escitalopram 54%, placebo 51%) **Mean age (year) (SD)**: - The mean age was 37 years (18-78), escitalopram 36 (18-78), placebo 38 (19-68) - The mean age at generalized SAD onset was 17 years. The mean duration of generalized SAD was 20 years. **Deinition of remission**: Patients were responded if Clinical Global Impressions-Improvement scale [CGI-I] score of 1 or 2. **Inclusion criteria:** Patients were mainly recruited via advertisements by psychiatrists in private or hospital outpatient clinics or by specialized clinical research centers. The inclusion criteria were for female and male outpatients between 18 and 80 years of age with a primary diagnosis of generalized SAD according to DSM-IV criteria.27 At the screening visit, patients were included if they had a total score 28,29 of ≥ 70 on the Liebowitz Social Anxiety Scale (LSAS),28 in line with previous studies,30 with exhibited fear or avoidance traits in at least 4 social situations, and had a. score of ≥ 5 on 1 or more of the Sheehan Disability Scale (SDS)[3]1 subscales. **Exclusion criteria**: Patients were excluded if they had another Axis I disorder that was considered the predominant diagnosis within the previous 6 months. Patients with a severity of depressive symptoms that may be thought likely to respond to an antidepressant (Montgomery-Asberg Depression Rating scale [MADRS] total score of ≥ 18) were excluded in order to test the efficacy of escitalopram on generalized SAD directly. Patients were excluded if they scored ≥ 5 on MADRS item 10 (suicidal thoughts). Other exclusions were DSM-IV diagnosis of alcohol or drug abuse, an eating disorder, MDD, PD, obsessive-compulsive disorder, body dysmorphic disorder, schizophrenia/other psychotic disorder, mania or hypomania or history thereof, and presence of an Axis II diagnosis. Patients with a known lack of therapeutic response to any SSRI were excluded. Treatment with a psychoactive drug within 2 weeks (5 weeks for fluoxetine) before screening was excluded. Patients who in the prior 2 weeks had received or who planned to initiate formal psychotherapy were not eligible.
Interventions	Escitalopram group (N=191) vs Placebo group (N=181)
Outcomes	**Relapse**: - Relapse was defined as either an increase in LSAS total score of ≥ 10 or withdrawal due to lack of efficacy, as judged by the investigator. - The relapse criteria were defined as either an increase in LSAS total score of ≥ 10 points over the score at randomisation or withdrawal of the patient from the study due to an unsatisfactory treatment response (lack of efficacy), as judged by the investigator. - The primary efficacy parameter was the survival analysis estimate of time to relapse in the double-blind period. - The secondary efficacy parameters were based on the LSAS total scores, the LSAS avoidance and fear/anxiety sub scale scores, and the SDS scores (work, social life, and family life). The CGI-I scores were recorded only in the open-label period. - Efficacy analyses were based on the intention-to-treat (TTT) population,

	which comprised all randomised patients who took at least 1 dose of double-blind study medication and who had at least 1 valid post baseline assessment of the LSAS total score. - The primary efficacy analysis, comparing relapse in the 2 treatment groups, was based on a log-rank test for survival data. As a supplement, Kaplan-Meier survival curves were produced, and the Cox proportional hazards model for survival data was used to estimate differences in relapse rates, hazard ratios, and median time to relapse and to evaluate the potential influence of covariate and subgroups. Ax^2 test was used to compare the crude proportions of relapsed patients. - The secondary efficacy parameters were analysed at week 24 using analysis of covariance, adjusting for canter and randomisation baseline values. the secondary analysis of relapse rates, based on the Cox proportional hazards model, Safety and Tolerability - Safety and tolerability were evaluated based on spontaneously reported adverse events, electrocardiograms (ECGs), vital signs (systolic and diastolic blood pressure and pulse rate), weight, physical examinations, and clinical safety laboratory tests (hematology and biochemistry). The 43-item Discontinuation Emergent Signs and Symptoms (DESS) checklist was used (after the general open questioning used for the recording of adverse events) at the end of the open-label period (at randomization) and 1 and 2 weeks after randomization. - Safety analyses in the open-label period were based on all patients who took at least 1 dose of escitalopram. The comparison of escitalopram with placebo in long-term treatment was made using the randomised population who had taken at least 1 dose of medication. - Response and tolerability were assessed after 1, 2, 4, 8, and 12 weeks of open-label treatment, and 1, 2, 4, 8, 12, 16, 20, and 24 weeks after randomisation to double-blind treatment. A safety follow-up was carried out 4 weeks after the last dose of double-blind treatment.
Notes	Funding: This study was sponsored by H. Lundbeck A/S. Conflictof interest : Dr. Montgomery has served as a consultant for and on the speakers or advisory boards of Lundbeck, Wyeth, GlaxoSmithKline, Pfizer, and Roche. Dr. Boulenger has served as a consultant for AstraZeneca, GlaxoSmithKline, Sanofi-Synthelabo, Eli Lilly, and Janssen and on the speakers or advisory boards of Lundbeck and Wyeth. Drs. Dürr-Pal, Loft, and Nil are employees of Lundbeck.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned in a 1:1 ratio using a computer-generated randomisation list to 24 weeks of double-blind treatment with escitalopram or an abrupt switch to placebo.
Allocation concealment	Low risk	The study medications were tablets for oral administration, of identical appearance, taste, and smell.

(selection bias)		
Blinding of participants and personnel (performance bias)	Unclear risk	Not reported
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	High risk	A total of 86 patients (17%) withdrew during the 12-week open-label period. Double-blind, placebo-controlled relapse prevention period. The overall discontinuation rate, excluding relapses, was 13.2% for patients treated with escitalopram (25 patients), and 8.3% for patients treated with placebo (15 patients).
Selective reporting (reporting bias)	Low risk	Discontinuation symptoms mentioned
Other bias	Low risk	Comment: study appears to be free from other sources of bias

Reimherr 1998

Methods	**Design:** multi-phase double-blind parallel 4 arm randomised placebo-controlled trial **Prerandomisation:** 12-14 weeks Duration post randomisation:50 weeks. 395 were randomly assigned to one of four arms of a double-blind treatment study (50 weeks of placebo, 14 weeks of fluoxetine and then 36 weeks of placebo, 38 weeks of fluoxetine and then 12 weeks of placebo, or 50 weeks of fluoxetine) Aim: The purpose of this study was to determine prospectively the optimal length of therapy in a long-term, placebo-controlled continuation study of patients who responded to acute fluoxetine treatment for major depression (defined by DSM-III-R). met the DSM-III-R criteria for major depression with duration of at least 1 month.
Participants	**Country:** five outpatient psychiatric clinics in the United States. **Setting**: five outpatient psychiatric clinics in the United States **Type of AD**: fluoxetine Duration of antidepressant treatment pre randomisation: 12-14 weeks of open-label acute fluoxetine therapy, 20mg/day (N=395 of 839 patients) were randomly assigned to one of four arms of a double-blind treatment study (50 weeks of placebo, 14 weeks of fluoxetine and then 36 weeks of placebo, 38 weeks of fluoxetine and then 12 weeks of placebo, or 50 weeks of fluoxetine) **Duration of antidepressant treatment post stabilisation**: 50 weeks **Total number of randomised participants**: 395 **Primary diagnosis: major depression** (defined by DSM-III-R). Severity of depressive symptoms at randomisation Modified Hamilton depression scale score, mean (SD): 21.5 placebo SD (3.7), fluoxetine 14w 20.5 SD(3.4) , fluoxetine 38w 20.5 SD (3.6), fluoxetine 50w 21 SD (3.6)

	Gender distribution (M)(F): placebo 77 SD (80.2), fluoxetine 14w 63 SD(64.9) , fluoxetine 38w 70 SD (70), fluoxetine 50w 64 SD (62.7) **Mean age, years(M)**: placebo 40.5 SD (10.5), fluoxetine 14w 40.1 SD(9.6) , fluoxetine 38w 40.3 SD (9.8), fluoxetine 50w 40.3 SD (11.2) **Inclusion** : 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. Allpatients had a modified 17-item Hamilton Depression Rating Scale(17) score of at least 16. The modified 17-item Hamilton scale was derived from a 28-item Hamilton depression scale that contained three extra items dealing with oversleeping and two dealing with overeating and weight gain Depressed patients with type II bi-polar disorder could be included if they met other entry criteria **exclusion:** Patients with type I bipolar disorder were excluded from the study
Interventions	395 were randomly assigned to one of four arms of a double-blind treatment study (50 weeks of placebo, 14 weeks of fluoxetine and then 36 weeks of placebo, 38 weeks of fluoxetine and then 12 weeks of placebo, or 50 weeks of fluoxetine) no tapering
Outcomes	1 -Relapse rate was the primary outcome measure. relapse rates were assessed in three fixed 12-week intervals after double-blind transfers from fluoxetine to placebo at the start of the double-blind period and after 14 and 38 weeks of continued fluoxetine treatment 2 -Remission was defined as no longer meeting the DSM-III-R cerite-riae for major depression and having a Hamilton depression scale to-tal score less than 7 for 3 consecutive weeks, both of which were to be maintained until the end of the acute therapy phase. Patientswho did not meet the remission criteria by week 9 could have the acute therapy phase extended for up to 2 weeks if their Hamilton depression score was 10 or less and had decreased 50% or more from baseline.
Notes	funding: Supported by a grant from Lilly Research Laboratories. Potential conflicts of interest: not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not enough information to permit a judgement
Allocation concealment (selection bias)	Unclear risk	Comment: not enough information to permit a judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: not enough information to permit a judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: not enough information to permit a judgement
Incomplete outcome data	Unclear risk	Comment: not enough information to permit a

(attrition bias)		judgement
Selective reporting (reporting bias)	High risk	Comment: protocol is not available; . Adverse events were not reported. Withdrawal symptoms were not an outcome.
Other bias	Low risk	no other bias

Robinson 1991

Methods	**Design:** RCT **Duration Prerandomisation phase**: acute treatment 6-13 weeks responders have continuation treatment for 16 weeks **Duration post randomisation**: 2 years **Aim:** A study is reported comparing the effectiveness of maintenance treatment with phenelzine in responding major depression patients. If they responded initially to non blind phenelzine treatment and sustained remission for 16 weeks, patients were randomised to 2-year double-blind treatment with phenelzine 60 mg/day, phenelzine 45 mg/day, or placebo.
Participants	**Country:** USA **Setting:** Marshall university Mood disorders clinic, outpatient facility for the study and treatment of affective disorders of the department of psychiatry **Type of AD:** phenelzine **Duration of antidepressant treatment pre randomisation**: acute treatment 6-13 weeks responders have continuation treatment for 16 weeks **Duration of antidepressant treatment post stabilisation**: 2 years **Number of participants**: 235 patient were screened for the study. of these, 88 met entry criteria. of the 88 patients initially started on phenelzine 15 were felt to nonresponder. 73 patient entered continuation therapy; 26 of these were judged incomplete resonders. 47 remaining patients maintained therapeutic benefit for the requisite 16 weeks **Total numbers of randomised participants**: 47 patients placebo (n= 16) phenelezine 45mg/day(n= 12) or phenelezine 60 mg/day (n= 19) **Primary diagnosis**: major depression disorder **Gender distribution : M/**F placebo 3/13 phen 45 2/10 phen 60 4/15 **Mean age, years:** placebo 43 ± 3 phen 45 43±4 phen 60 43±2 Severity of depressive symptoms at randomisation: HAM-D 17-item placebo 3.5 ± 1.5 phen 45 3.5.±1.0 phen 60 3.6± 0.9

	Inclusion criteria: Criteria entered the study diagnosis of major depressive disorder using Research diagnostic criteria RD, !&- item Hamilton rating scale> 18, Raskin Depression scale score > 7 and 5 a history of an antecedent episode of either RDC major of minor depression Exclusion criteria: remission period of less than 20 weeks between the present in a previous episode, presence of a major noninfective psychiatric disorder, history of mania of hypomania, history of alcohol or substance abuse during the year prior to pregnancy
Interventions	phenelzine versus placebo
Outcomes	1- Relapse (define as return of depressive symptoms less than 3-month post randomisation) or recurrence define as return of depression syndrome at least 3-months post randomisation to be documented on two successive clinical evaluations patients were seen monthly during 2 years of maintenance and more frequently if clinically indicated. emergence of symptoms of insufficient intensity to meet criteria for relapse 2- treatment- emergent symptoms were rated as mild,moderate or sever possible drug side effect were regarded as symptoms not present before treatment and unlikely manifestations of the depression
Notes	Study funding sources: Marshall university

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not enough information to judge
Allocation concealment (selection bias)	Unclear risk	Comment: not reported
Blinding of participants and personnel (performance bias)	Low risk	47 patients were randomly assigned to double-blind treatment.
Blinding of outcome assessment (detection bias)	Low risk	Comment: described as double-blind (in Kocsis 2007); unlikely that blinding could have been broken the acute treatment patients were evaluated every week or as clinically indicated HAM-D, GAS, AND and Raskin scale rating sheets and progress notes including side effect where complete at each visit patients were seen monthly during the 2 years of maintenance and more frequently if clinically indicated
Incomplete outcome data (attrition bias)	High risk	Comment: high rate of missing although reasons reported, still high dropout. Number of participants: 235 patient were screened for the study. of these, 88 met entry criteria. of the 88 patients initially

		started on phenelzine 15 were felt to nonresponder. 73 patient entered continuation therapy; 26 of these were judged incomplete responders. 47 remaining patients maintained therapeutic benefit for the requisite 16 weeks from this 47 patient only 13 patient complete 2 years maintenance treatment
Selective reporting (reporting bias)	High risk	Comment: adverse events reported but; no information on withdrawal symptoms reported
Other bias	Low risk	Comment: study appears to be free from other sources of bias

Rosenthal 2013

Methods	Design: , multicenter, double-blind, placebo controlled, parallel-group, randomised withdrawal study Prerandomisation phase: 8-week open-label response phase and 12-week open-label stabilization phase **Duration post randomisation:** the 6- month double-blind period. **Aim:** Evaluate the long-term (11-month) efficacy and safety of desvenlafaxine (administered as desvenlafaxine succinate) at the recommended 50-mg/d dose in preventing relapse in patients with major depressive disorder (MDD)
Participants	**Country**: 14 countries worldwide (North America, 30; South America, 10; Europe, 44; South Africa, 3) **Setting**: study was conducted at 87 study sites in 14 countries worldwide (North America, 30; South America, 10; Europe, 44; South Africa, 3) **Type of AD**: Desvenlafaxine **Duration of antidepressant treatment pre randomisation**: 8-week open-label response phase and 12-week open-label stabilization phase **Duration of antidepressant treatment post stabilisation**: the 6- month double-blind period **Number of participants**: A total of 874 patients were enrolled in open label phase **Total numbers of randomised participants**: 548 patients were randomly assigned to receive placebo (n = 276) or desvenlafaxine 50 mg/d (n = 272) in the double-blind withdrawal period. primary diagnosis: Major Depressive Disorder **Gender distribution (women):** Open-Label Desvenlafaxine (N = 874): 608 (69.6) Double-Blind Placebo (n = 276): 198 (71.7) Desvenlafaxine (n = 272): 193 (71.0) **Mean age, years (SD):** Open-Label Desvenlafaxine (N = 874): 45.0 ± SD13.3 Double-Blind Placebo (n = 276): 45.3 ± SD 13.0 Desvenlafaxine (n = 272): 46.6 ± SD 13.0 **Severity of depressive symptoms at randomisation**: HDRS17 total score, mean ± SD placebo: 24.3 ± 2.8

	Desvenlaxafine : 23.9 ± 2.6 **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 (HDRS17)30 total score ≥ 20, a HAM-D17 item 1 (depressed mood) score ≥ 2, and a Clinical Global Impressions-Severity of Illness scale (CGI-S)31 score ≥ 4 at screening and baseline visits **Exclusion criteria:** 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 HDRS17 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 Interview32 and a psychiatric interview), or clinically important medical disease
Interventions	Desvenlafaxine versus placebo Patients who were randomly assigned to receive placebo were tapered to double-blind treatment with desvenlafaxine 25 mg/d during the first week of the double-blind period.
Outcomes	1- The primary outcome for the study was time to relapse following randomisation to the double-blind period. Relapse was defined as any 1 (or more) of the following: HDRS17 total score ≥16, discontinuation for unsatisfactory tory response (including the need for additional/alternate treatment for depression, investigator decision to remove the patient from the study for efficacy reasons, or failure to return if the investigator determined it was related to efficacy), hospitalisation for depression, suicide attempt, or suicide 2- secondary outcome is safety en Tolerability. Safety was assessed throughout the open-label and double-blind periods. Safety assessments included vital signs (supine and standing blood pressure, pulse rate, body weight, and height), laboratory determinations, 12-lead electrocardiogram (ECG) recordings, monitoring of adverse events (AEs; categorized based on Medical Dictionary for Regulatory Activities [MedDRA]33 terminology), withdraw- als due to AEs, concomitant medications, and administration of the Columbia-Suicide Severity Rating Scale (C-SSRS). 3- Efficacy: The primary efficacy analysis assessed time to relapse from randomisation to double-blind treatment for desvenlafaxine compared with placebo using the log-rank test
Notes	study funding: This study was sponsored by Pfizer Inc. Medical writing support was provided by Kathleen M. Dorries, PhD, at Peloton Advantage and was funded by Pfizer Inc. potential conflicts of interest: Dr Boyer has been on a speakers/advisory board for Servier, has been a consultant to Institut de Recherche Pierre Fabre, and has received honoraria from Pfizer. Ms Vialet and Dr Hwang are

	employees of Pfizer, and Dr Tourian is an employee of and stock shareholder in Pfizer. Dr Rosenthal reports no potential conflict of interest.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned to treatment based on subject randomisation numbers accessed by site personnel through a centralized, computerized treatment assignment system.
Allocation concealment (selection bias)	Unclear risk	information insufficient to permit judgement
Blinding of participants and personnel (performance bias)	Low risk	This study double-blind, placebo-controlled, randomized withdrawal trial assessed the long-term efficacy of the recommended 50-mg/d desvenlafaxine dose.
Blinding of outcome assessment (detection bias)	Low risk	Comment: blinding of outcome assessment ensured; unlikely that the blinding could have been broken patient e were eligible to enter the double-blind treatment period. Eligible patients were randomly assigned 1:1 to receive 6-month treatment with placebo or desvenlafaxine 50 mg/d during the double-blind, randomised withdrawal period. A follow-up visit was scheduled approximately 7 days after the last tapered dose. Patients completed the HDRS17 and CGI-I at double-blind. period weeks 1, 2, 3, 4, 6, 10, 14, 18, 22, and 26
Incomplete outcome data (attrition bias)	High risk	high rate of dropout from placebo groep 276 patient 100 is missing from medicatie groep 272 patient 62 is missing
Selective reporting (reporting bias)	High risk	the study protocol is available. Most predefined primary and secondary outcomes were reported in a predefined way. Withdrawal symptoms were not reported
Other bias	Unclear risk	Comment: a grant from the pharmaceutical industry several study limitations should be noted. First, the inclusion and exclusion criteria used in this study selected for a population of generally healthy patients with a primary diagnosis of MDD. Findings therefore may not generalize to a broader population of depressed patients with other clinical characteristics. A possible limitation of the study design (randomizing desvenlafaxine-treated patients to placebo in the double-blind period) was the potential for confounding discontinuation symptoms and symptoms of relapse, as the placebo group had their previous desvenlafaxine dose tapered in the first week of the double-blind period.42 However, the sensitivity analyses, which excluded data from the first weeks of the double-blind period (when discontinuation symptoms were most likely to occur43), were included in the study design specifically to address this potential limitation. Third, the trial

		duration was less than 1 year (11 months); there remains a need for efficacy and safety data for desvenlafaxin

Stein 2012

Methods	**Design**:RCT Prerandomisation phase: open label study 16-week patient treated with agomelatine 25–50 mg/dag **Duration post randomisation:** 26 weeks patient were randomly assigned to receive continuation treatment with agomelatine (n = 113) or placebo (n = 114) **Aim**: The present study was performed in non depressed GAD patients to evaluate the longerterm efficacy and tolerability of agomelatine. After an initial response to agomelatine, time to relapse was assessed in patients randomised to treatment with agomelatine versus placebo during a 6-month maintenance period.
Participants	**Country:** The study was undertaken in 31 clinical enters in Canada, Denmark, Estonia, Finland, Hungary, and Sweden Setting: patients were recruited by advertisement (64.8%), selfreferral (17.6%), or referral by a psychiatrist (5.2%), a psychologist (0.4%), general practitioner, or other specialist (12%). **Type of AD:** agomelatine **Duration of antidepressant treatment pre randomisation**: patient treated with agomelatine 25–50 mg/dag for 16 weeks **Duration of antidepressant treatment post stabilisation**: 43 weeks primary disease:General anxiety disorder **Number of participants:** Of the 477 patients entering the openlabel period, 329 (69.0%) completed the openlabel period, **Total numbers of randomised participants**: DoubleBlind Period Agomelatine (n = 113), Placebo (n = 114) total 227 **Gender distribution (male/ female ratio):** OpenLabel Period Agomelatine (N = 477) 36.9/63.1 DoubleBlind Period Agomelatine (n = 113) 37.2/62.8 ,Placebo (n = 114) 38.6/61.4 **Mean age, years (SD):** OpenLabel Period Agomelatine (N = 477) 44.8 ± 14. DoubleBlind Period Agomelatine (n = 113) 45.9 ± 14.0 ,Placebo (n = 114) 47.0 ± 15.1 Severity of depressive symptoms at randomisation: Start of the Double-Blind Period (week 16) HARS Agomelatine 5.9 ± 2.7, placebo 6.0 ± 2.6 CGI Agomelatine 1.8 ± 0.7, placebo 1.8 ± 0.8 HAD for anxity Agomelatine 6.1 ± 3.4, placebo 6.0 ± 3.0, for depression 3.5

	± 2.8, 3.0 ± 3.0 respectively **Inclusion criteria** Patients aged at least 18 years were required to have a screening 14item HARS total score ≥ 22, with HARS item 1≥2anditem2≥2,withthesumofHARSitem1anditem 2 ≥5; a Montgomery-Asberg Depression Rating Scale15 (MADRS) total score ≤ 16; and a decrease of < 20% in HARS total score between screening and baseline. Patients were required to be physically healthy or to have stabilized somatic illnesses **Exclusion criteria** Patients with any of the follow ing disorders from DSM-IV-TR, identified with the MINI, were excluded: panic disorder, posttraumatic stress disorder, agoraphobia, social phobia, obsessivecompulsive disorder, or psychiatric disorder other than GAD (within 6 months prior to the selection visit). Patients were excluded when there was evidence of ongoing alcohol or drug abuse or any personality disorder that might compromise the study, if they were at risk of suicide, had a score > 3 on item 10 of MADRS, or reported a suicide attempt within the past year. Patients with a current GAD episode resistant to at least 2 different previous antianxiety treatments during the past 12 months were also excluded. patients were excluded if they had received any of the following recent/concomitant therapies: psychotherapy of any type started within 30 days prior to the selection visit and during the study or anxiolytics or antipsychotics taken within 1 week prior to the selection visit.
Interventions	Agomelatine versus placebo
Outcomes	1- outcome: time to relapse Efficacy and tolerability parameters were assessed at inclusion and after 2, 4, 8, 12, and 16 weeks of openlabel treatment; 4 weeks after week 16; and then every 4 weeks (2 weeks for the 2 last visits) until week 42. The HARS was rated at each visit up to week 42 or in case of premature withdrawal. the primary endpoint of efficacy was relapse occurring within 6 months from randomisation and defined either by a HARS total score ≥ 15 or by clinical judgment of a lack of efficacy. The main outcome measure was the time to relapse during the maintenance period (time between randomisation and relapse date). 2-Secondary efficacy parameters included HARS total score, HARS psychic and somatic anxiety sub score, and Clinical Global ImpressionsSeverity of Illness (CGIS) and Global Improvement (CGII) scores.16 The CGIS was assessed at each visit up to week 42 or in case of premature withdrawal. During the openlabel period, the CGII was compared between weeks 0 and 2; during the maintenance period, it was compared to the value at week 16. 3-The tolerability and safety evaluations were based on emerging adverse events (AEs) spontaneously reported by the patient or elicited by the investigator from week 0, vital signs (blood pressure, heart rate, and weight), biochemistry and

	hematology parameters, and 12lead electrocardio gram abnormalities. Liver enzyme values were monitored until return to normal values if > 3 times the upper limit of the reference range for aspartate aminotransferase/alanine aminotransferase (AST/ALT) and > 2 times the upper limit of the reference range for total bilirubin. At week 42, agomelatinetreated patients were reran domized either to receive either placebo or to continue agomelatine (same dose) during 1 week to evaluate dis continuation symptoms on the 43item Discontinuation Emergent Signs and Symptoms checklist (DESS).
Notes	Funding support: This study was sponsored by Servier (Suresnes, France). Potential conflicts of interest: Dr Stein has received research grants and/or consultancy honoraria from Abbott, AstraZeneca, Eli Lilly, GlaxoSmithKline, Jazz, Johnson & Johnson, Lundbeck, Orion, Pfizer, Pharmacia, Roche, Servier, Solvay, Sumitomo, Takeda, Tikvah, and Wyeth. Dr Ahokas has received research grants and/or consultancy honoraria from AstraZeneca, BristolMyers Squibb, Eli Lilly, GlaxoSmithKline, Lundbeck, Orion, Otsuka, SanofiAventis, Servier, and Wyeth. Drs Albarran and Olivier are employees of Servier. Dr Allgulander is an employee of Karolinska Institutet, the School of Medicine, Stockholm, Sweden; a speaker for Servier, Eli Lilly, AstraZeneca, and Pfizer; and an advisory board member of Pfizer Sweden.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	After the open-label period, eligible patients were assigned to agomelatine or placebo treatment in a 1:1 ratio according to a balanced (nonadaptive) randomization with stratification by center.
Allocation concealment (selection bias)	Low risk	During the study, all patients took 2 tablets orally daily in the evening. The dosage schedule and the appearance and taste of study treatment were the same for all patients
Blinding of participants and personnel (performance bias)	Low risk	This study began with a 16-week open-label treatment period that was followed by a 26-week, randomized, double-blind, placebo-controlled maintenance treatment period.
Blinding of outcome assessment (detection bias)	Low risk	Comment: blinding of outcome assessors (doctors); blinding unlikely to have been broken y efficacy parameters included HARS total score, HARS psychic and somatic anxiety subscore, and Clinical Global Impressions-Severity of Illness (CGI-S) and Global

		Improvement (CGI-I) scores.16 The CGI-S was assessed at each visit up to week 42 or in case of premature withdrawal.
Incomplete outcome data (attrition bias)	Low risk	All missing data accounted for and reasons for dropouts reported
Selective reporting (reporting bias)	High risk	study protocol are available; adverse events reported but withdrawal symptoms are not reported; they are a fundamental outcome in drug discontinuation studies
Other bias	Unclear risk	Comment: a grant from the pharmaceutical industry

Stewart 1998

Methods	**Design:** RCT Prerandomisation phase: 12 weeks open trial of fluoxetine Duration post randomisation: 50-week randomised placebo substitution trial **Aim:** Three hypotheses were studied: Patients with a true drug response pattern will relapse more often while taking placebo than while taking continued medication. The relapse rates of patients with a placebo pattern of response will not depend on treatment. While continuing to receive fluoxetine, patients with placebo response patterns will relapse more frequently than patients with true drug response patterns.
Participants	**Country:** USA **Setting:** outpatients a multisite study designed to determine the optimal duration of fluoxetine treatment. Five sites enrolled patients with major depression into an open, 12-week trial of fluoxetine **Type of AD**: fluoxetine, **Duration of antidepressant treatment pre randomisation**: 12 weeks **Duration of antidepressant treatment post stabilisation**: not reported **Total number of randomised participants**: 392 Responders were randomly assigned within site by a computer-generated code to 1 of 4 groups: 1, immediate placebo substitution;(95) 2, continuation of fluoxetine therapy for 14 weeks followed by placebo substitution: (96) 3, continuation of fluoxetine therapy for 38 weeks followed by placebo substitution: (99) or 4, continuation of fluoxetine therapy for 50 weeks.: (102) After randomisation, treatment was double-blind and patients were seen weekly for 2 weeks, then biweekly for 16 weeks, and then monthly. Extra visits were scheduled if depressive symptoms returned. Relapse was defined as either (1) an mHAMD score of 14 or more for 3 consecutive

	weeks or (2) having met the DSM-III-R criteria for major depression for 2 consecutive weeks. **Primary diagnosis:** major depression (research diagnostic criteria) Severity of depressive symptoms at randomisation, mean (SD) Remission was defined as an mHAMD score of 7 or less and failure to meet the DSM-III-R criteria for major depression after each of the last 3 weeks of the 12-week trial **Average age of onset of depressive disorder**: range 18 to 65years **Comorbidity**: Not described **Gender distribution (F):** 269 (69 percent of patients) **Mean age, years (SD)**: range 18 to 65years **Definition of remission**: Remission was defined as an mHAMD score of 7 or less and failure to meet the DSM-III-R criteria for major depression after each of the last 3 weeks of the 12-week trial **Inclusion criteria**: All study subjects were outpatients aged between 18 and 65 years, were physically healthy, met the DSM-III-R22 criteria for major depression, and had a modified 17-item Hamilton Depression Rating Scale23 (mHAMD) score of 16 or more. The mHAMD substituted hypersomnia and hyperphagia for insomnia, anorexia, and weight loss items in patients with reverse vegetative symptoms. **Exclusion criteria** patients were excluded for unstable medical illnesses, pregnancy or lactation, serious suicidal impulses, history of psychosis, organic mental disorder, mania or antisocial personality disorder, substance abuse disorder in the past year, hypothyroidism, previous fluoxetine treatment for longer than 1 week in the current episode or longer than 3 months in a previous episode, or lack of a response to 8 weeks of treatment with fluoxetine hydrochloride, 20 mg/d.
Interventions	Intervention 1: placebo(, immediate placebo substitution) Intervention 2: continuation of fluoxetine therapy for 14 weeks followed by placebo substitution Intervention3: continuation of fluoxetine therapy for 38 weeks followed by placebo substitution; Intervention 4: continuation of fluoxetine therapy for 50 weeks. Co-intervention: Not reported
Outcomes	The primary analysis for each hypothesis tested whether relapse during weeks 12 to 26 differed between comparison groups. The log-rank test assessed Kaplan-Meier survival curves for differences in time to relapse between groups. Secondary analyses included similar Kaplan-Meier analyses for weeks 26 to 50 and 50 to 62. All analyses were performed for the period immediately following each placebo substitution point (ie, 12, 26, and 50 weeks) until the next substitution point or end of the study. Analyses testing hypothesis 1 compared patients with the true drug pattern randomized to group 1 (placebo) (n=63) with those randomized to groups 2 through 4 (continued fluoxetine therapy) (n=191) for weeks 12 to 26

	(primary analysis); those in group 2 (placebo) (n=41) with those in groups 3 and 4 (continued fluoxetine therapy) (n=69) for weeks 26 to 50; and those in group 3 (placebo) (n=26) with those in group 4 (continued fluoxetine therapy) (n=19) for weeks 50 to 62 (secondary analyses). For hypothesis 2, analyses compared patients with the placebo pattern randomized to group 1 (placebo) (n=32) with those randomised to groups 2 through 4 (continued fluoxetine therapy) (n=106) for weeks 12 to 26 (primary analysis); those in group 2 (placebo) (n=11) with those in group 3 or 4 (continued fluoxetine therapy) (n=37) for weeks 26 to 50; and those in group 3 (placebo) (n=8) with those in group 4 (continued fluoxetine therapy) (n=9) for weeks 50 to 62 (secondary analyses). Analyses for hypothesis 3 compared fluoxetine-treated patients with a true drug pattern with fluoxetine-treated patients with a placebo pattern. This was groups 2 through 4 (n=191 and n=106) for weeks 12 to 26 (primary analysis) and groups 3 and 4 (n=69 and n=37) for weeks 26 to 50 and group 4 (n=19 and n=9) for weeks 50 to 62 (secondary analyses) (the first n values are for patients with a true drug pattern of initial response, and the second n values are for patients with a placebo pattern of initial response).
Notes	Funding: Eli Lilly Corp, Indianapolis, Ind, sponsored the study COI: not described

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Responders were randomly assigned within site by a computer-generated code to 1 of 4 groups: 1, immediate placebo substitution; 2, continuation of fluoxetine therapy for 14 weeks followed by placebo substitution; 3, continuation of fluoxetine therapy for 38 weeks followed by placebo substitution; or 4, continuation of fluoxetine therapy for 50 weeks.
Allocation concealment (selection bias)	Unclear risk	Opaque envelopes contained each patient's treatment code, to be opened only in an emergency. Otherwise, the treatment code was known only to Eli Lilly Corp staff not involved with clinical decisions.
Blinding of participants and personnel (performance bias)	Unclear risk	Opaque envelopes contained each patient's treatment code, to be opened only in an emergency. Otherwise, the treatment code was known only to Eli Lilly Corp staff not involved with clinical decisions.
Blinding of outcome assessment (detection bias)	Unclear risk	not reported
Incomplete outcome data (attrition bias)	Unclear risk	not reported
Selective reporting (reporting bias)	High risk	No discontinuation symptoms mentioned. withdrawal symptoms were not reported.
Other bias	Unclear risk	Funding: Eli Lilly Corp, Indianapolis, Ind, sponsored the study

		COI: not describe

Thase 2001

Methods	**Design:** RCT Prerandomisation phase: No fewer than 8 and no more than 12 weeks of treatment were permitted in which to meet these criteria. Patients not remitting were withdrawn from the protocol at week 12 Duration post randomisation: Patients who met remission criteria were eligible to enter the 40-week double-blind continuation-phase protocol **Aim:** the current study was performed to evaluate the efficacy and safety of up to 1 year of mirtazapine therapy, using a more rigorous, randomised, placebo-controlled discontinuation design.
Participants	**Country**:This study was conducted at 12 clinical research centres across the United States **Setting:** 12 clinical research centres **Type of AD**: mirtazapine **Duration of antidepressant treatment pre randomisation:** No fewer than 8 and no more than 12 weeks of treatment were permitted in which to meet these criteria. Patients not remitting were withdrawn from the protocol at week 12 **Duration of antidepressant treatment post stabilisation**: Patients who met remission criteria were eligible to enter the 40-week double-blind continuation-phase protocol **Number of participants**: A total of 421 patients enrolled in the acute-phase trial, of which 418 began open-label mirtazapine therapy and were included in the safety analyses. Of those beginning therapy, 410 (98%) completed at least one post baseline assessment and were included in the acute-phase efficacy analyses. An acute-phase therapy remission rate of 43% (178/410) was observed Open-label phase ITT 410 Total numbers of randomised participants: A total of 161 (90%) of the 178 fully remitted patients were randomly assigned to begin double- blind therapy. (17missed) Of the 17 patients not randomly assigned, 15 were not enrolled in the double-blind study because the enrollment goal was met, and 2 declined further participation. Five additional patients dropped out before the first follow-up visit on double-blind therapy. The ITT sample for the double-blind continuation phase thus consisted of 156 patients. Double-Blind Phase Mirtazapine (N = 76) Placebo (N = 80) **Gender distribution** (F): female, Open Label Period Mirtazapin 230 from total 410, SD 56.1 Double Blind Period Mirtazapin 40 SD 52.6 Double Blind Period Placebo 39 SD 48.8 **Primary diagnosis**/ Chronic MDD en Recurrent MDD **Mean age, years (SD): mean age =** 39.5 year Severity of depressive symptoms at randomisation:

	HAM-D score Mirtazapine (N = 76): 6.1 (7.2) placebo: (N = 80): 10.7 (8.8) CGI score at end of phase, mean (SD) Mirtazapine (N = 76): 1,6 (1.1) placebo: (N = 80): 2.3 (1.3) **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. Potentially eligible patients had to be in reasonably good 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 permit- ted 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 minimally effective doses) of any approved antidepressant in the cur- rent 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. Potentially eligible patients had to be in reasonably good health, not have abused drugs or alcohol for at least 3 months before enrolment and provide explicit written informed consent. Severity of depressive symptoms at randomisation, mean (SD): Hamilton Rating Scale for Depression and Clinical Global Impressions-Improve- ment scores
Interventions	mirtazapine versus placebo
Outcomes	1-primary outcome: relapse was defined a priori by any one of the following criteria: (1) HAM-D score ≥ 18, (2) HAM-D scores of ≥ 15 at 2 consecutive weekly visits, or (3) any suicide attempt or suicide. 2- secondary outcome Adverse events were recorded by the treating psychiatrist according to standard conventions. The query "Have you experienced any adverse events or side effects

	since your last visit?" was used to elicit the patient's spontaneous reports. Both new-onset adverse events and those that persisted from visit to visit were recorded. 3- Tolerability and safety Acute-phase therapy with mirtazapine was initiated at 15 mg/day, with titration to 30 mg/day permitted after at least 1 week. A maximum dose of 45 mg/day was allowed after at least 2 weeks of therapy. Patients were seen for follow-up visits after 1, 2, 3, 4, 6, 8, and (if necessary) 10 and 12 weeks of therapy. Continuation-phase visits were required at monthly intervals, although interim visits were permitted if clinically indicated (i.e., if an increase in depressive symptoms occurred). When patients scored ≥ 15 on the HAM-D, interim visits were scheduled within 1 week. The physical examination, ECG, and laboratory studies were repeated at the endpoint of double-blind therapy.
Notes	Funding: funded by pharmaceutical industry COI: study author works for pharmaceutical company that funded the trial

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	insufficient information to judge about the sequence generation
Allocation concealment (selection bias)	Low risk	double-blind continuation-phase treatment was randomly assigned, with approximately 50% of the patients switched immediately from active mirtazapine to identically appearing placebo tablets.
Blinding of participants and personnel (performance bias)	Low risk	Comment: study is described as double-blinded, and blinding appeared to be maintained
Blinding of outcome assessment (detection bias)	Unclear risk	comment: outcomes defined didnot used valid and reliable measures, implemented consistently across all the study participants our study did not require the use of structured diagnostic interviews to confirm eligibility or systematically identify comorbidities. Moreover, our primary definition of relapse was based on the investigators' impressions, not on an independent assessment according to standardized criteria
Incomplete outcome data (attrition bias)	Low risk	A total of 11.8% of patients (9/76) withdrew from double-blind mirtazapine therapy due to adverse events, as compared with 2.5% of patients (2/80) in the placebo group

Selective reporting (reporting bias)	High risk	Comment: the study protocol is available, and all of the study's pre-specified (primary and secondary) outcomes have been reported in the pre-specified way. Suspected serious adverse events were recorded and were reported to the ethics committee, although they were not mentioned in the report. With- drawal symptoms were not an outcome
Other bias	Unclear risk	Grant from pharmaceutical industry This study has several limitations that may influence interpretation of the results. First, we did not employ in- terim assessments during the initial weeks following the double-blind switch of mirtazapine to placebo. Conse- quently, although we observed no evidence of discontinu- ation symptoms following the abrupt withdrawal of mir- tazapine, our design was not sensitive enough to detect subtler, transient symptoms. Second, our study did not require the use of structured diagnostic interviews to confirm eligibility or systemati- cally identify co morbidities. Moreover, our primary defi- nition of relapse was based on the investigators' impres- sions, not on an independent assessment according to standardized criteria. Although these methodological limitations did not compromise testing of the study's hy- potheses, the use of standardized evaluations would have helped to ensure internal validity. Third, the external validity or generalizability of this randomized clinical trial is limited by the exclusion of patients with more severe comorbidities or prior treatment resistance, as well as by the loss of an unknown number of patients who were unwilling to consent to participate in a study in which placebo may be substituted for active medication. Ultimately, the results of randomized clinical trial studies must be placed beside the findings of less highly controlled investigations.

Walker 2000

Methods	RCT **Design:** double-blind randomised controlled trial Prerandomisation phase20 weeks **Duration post randomisation:** 24 weeks **Aim:** The aim of this study was to evaluate the efficacy, tolerability, and effects on quality of life of sertraline, a selective serotonin reuptake inhibitor, in the prevention of relapse of generalized social phobia
Participants	**Country:** Canada **Setting:** 10 outpatients anxiety clinics in Canada with generalized social phobia **Duration of antidepressant treatment prerandomisation:** 20 weeks **Duration of antidepressant treatment post stabilisation**:

	Number of participants: not mention **Total numbers of randomised participants**: 50 (25 placebo, 25 antidepressant) Primary diagnosis: generalized social phobia **Gender distribution (male/F):** sertraline 16/10 (60%/40%) placebo 17/8(68/32%) **Mean age, years (SD):** sertraline37.24 % . placebo 35.96 Severity of anxiety symptoms at randomisation, mean (SD) -GGIS : placebo 2.52(1.08), sertraline 2.40 (0.96) **Inclusion** criteria Inclusion criteria for the study required patients to meet DSM-IV criteria for primary generalized social phobia of at least 1 year's duration at screening with a CGI-Severity (CGI-S) score of 4 or greater (i.e., moderately ill or worse) and to be between 18 and 60 years of age without any serious or uncontrolled medical illness or condition that precluded sertraline use Patients with an additional diagnosis of avoidant personality were allowed to participate. Patients with comorbid major depression were permitted to enter the study provided that their diagnosis was the result of social phobia; their baseline Montgomery-Åsberg Depression Rating Scale (MADRS) score had to be 19 or less; the onset of social phobia had to predate the onset of the current episode of depression by 5 years or more; and they did not represent a significant suicide risk. Patients receiving benzodiazepines were permitted to enter the study after completing a minimum of 2 to 4 weeks of tapered discontinuation. **Exclusion** criteria Patients were excluded if they had another primary axis I disorder or if they fulfilled criteria in the previous 6 months for panic disorder, agoraphobia, obsessive-compulsive disorder, eating disorders, body dysmorphic disorder, or substance abuse. Other exclusion criteria included concomitant use prior to study screening of psychotropic medication within a period of five half-lives, neuroleptics within 7 months, serotonergic antidepressants or an antianxiety medication for 3 or more weeks within 3 months, and cognitive-behavior therapy within 4 weeks. Additional reasons for exclusion included a urinary screen positive for benzodiazepines at baseline; treatment with β-blockers, methyldopa, guanethidine, or clonidine; and participation in a clinical trial within the previous 12 months. Women who were pregnant, lactating, or not using an acceptable method of contraception were excluded, as were patients who had had a major life event in the last 3 months that, in the investigator's opinion, was influencing their current condition
Interventions	sertraline versus placebo
Outcomes	The aim of this study was to evaluate the efficacy, tolerability, and effects on quality of life of sertraline, a selective serotonin reuptake inhibitor, in the prevention of relapse of generalized social phobia 1_-The primary efficacy assessments were the following: the number of patients relapsing (CGI-S score increase of more than 2 points over

	continuation study baseline and/or discontinuation for lack of therapeutic effect); percentage of patients with a CGI-I score of 1 (very much improved) or 2 (much improved)20 evaluated relative to the CGI-S score at continuation study baseline (week 20); and the mean total score changes from continuation study baseline to endpoint on CGI-S, the patient-rated 5-item Social Phobia sub scale of the Marks Fear Questionnaire (MFQ),21 and the physician-rated 11-question Duke Brief Social Phobia Scale (BSPS) 2-Physician-rated secondary efficacy variables included the sub scales of the BSPS assessing fear-avoidance of and physiologic response to; performance and social situations; and overall severity of illness/clinical global improvement on the Overall Severity of Illness and Change Measure of the Liebowitz Panic and Social Phobic Disorders Rating Form that includes assessments on five sub scales assessing anxiety episodes, phobic avoidance, anticipatory anxiety, overall functional impairment, and social phobia. Patient-rated secondary efficacy variables included the Social Phobia and Anxiety Inventory25 total score and Social Phobia subscale; the Social Avoidance and Distress Scale, a measure of social avoidance and discomfort26; and the Fear of Negative Evaluation Scale Other scales assessed levels of depressive symptomatology (the physician-rated MADRS),27 general anxiety (the Clinical Anxiety Scale [CAS]),28 and quality of life (the Sheehan Disability Inventory [SDI]) 3- Safety assessments included the evaluation, at each visit, of vital signs (weight, blood pressure, and heart rate) and the recording of spontaneously reported or observed adverse events. In addition, the use of concomitant medication was recorded and compliance was monitored by pill counts of returned medication. The main efficacy analyses were performed using the change from baseline to visit and endpoint (last observation carried forward) during the 24-week continuation treatment period.
Notes	Funding: Pfizer Pharmaceutical Group, Pfizer Inc., New York, COI: not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	information insufficient to permit judgement
Allocation concealment (selection bias)	Unclear risk	information insufficient to permit judgement
Blinding of participants and personnel	Unclear risk	information insufficient to permit judgement

(performance bias)		
Blinding of outcome assessment (detection bias)	Unclear risk	information insufficient to permit judgement
Incomplete outcome data (attrition bias)	High risk	high rate of missing. 27 from 50 are dropout from the study
Selective reporting (reporting bias)	High risk	withdrawal symptoms not an outcome;
Other bias	Unclear risk	Comment: a grant from the pharmaceutical industry Further research should address questions of optimal dose, longer durations of treatment, and the potential usefulness of the addition or augmentation of cognitive-behavioral treatment to improve response and/or reduce relapse.

Wetherell 2013

Methods	**Design**:RCT **Prerandomisation phase:** the study provided treatment in three phases: acute, augmentation, and maintenance. In the acute phase, all participants were treated with 12 weeks of open-label escitalopram. They started at a dosage of 10 mg/day; the dosage was increased to 20 mg/day after 4 weeks as tolerated if symptoms were not improving. Duration post randomisation: 44 weeks At the end of 12 weeks, participants who exhibited at least a 20% improvement in HAM-A symptoms were eligible to be randomly assigned to one of four conditions 1) 16 weeks of escitalopram augmented with 16 sessions of CBT (augmentation phase), followed by 28 weeks of continued escitalopram (maintenance phase) 2) 16 weeks of escitalopram without CBT, followed by 28 weeks of continued escitalopram (maintenance phase) 3) 16 weeks of escitalopram plus CBT, followed by 28 weeks of pill placebo; or 4) 16 weeks of escitalopram without CBT, followed by 28 weeks of pill placebo. **Aim**:objective of the present study was to examine whether sequenced treatment with escitalopram and CBT boosts acute response and prevents relapse in older adults with generalized anxiety disorder
Participants	**Country:** USA **Setting:**Participants were recruited through primary care practices, mental health clinics, and advertisements at three sites: Pittsburgh, San Diego, and St. Louis. **Type of AD**: **Duration of antidepressant treatment prerandomisation**: 12 weeks **Duration of antidepressant treatment post stabilisation**: 44 weeks At the end of 12 weeks, participants who exhibited at least a 20%

	improvement in HAM-A symptoms were eligible to be randomly assigned to one of four conditions 1) 16 weeks of escitalopram augmented with 16 sessions of CBT (augmentation phase), followed by 28 weeks of continued escitalopram (maintenance phase) 2) 16 weeks of escitalopram without CBT, followed by 28 weeks of continued escitalopram (maintenance phase) 3) 16 weeks of escitalopram plus CBT, followed by 28 weeks of pill placebo; or 4) 16 weeks of escitalopram without CBT, followed by 28 weeks of pill placebo. **Number of participants:** A total of 86 participants were enrolled in the study 13 discontinued the study during the acute phase because of medication side effects or lack of efficacy, leaving a randomized sample of 73 participants. Total numbers of randomised participants: 37 primary diagnosis disease: generalized anxiety disorder **Mean age, years (SD):** Escitalopram Plus CBT (N=18) 70.5, SD7.7 Escitalopram only (N19) 70.3, SD 8,6 CBT Plus Placebo (N=1) 70,2 SD 8,1 Placebo Only (N=18) 66,9 SD 5.7 Gender disterubtion F Escitalopram Plus CBT (N=18) 12, SD 66,7 Escitalopram only (N19) 14 SD 37,7 CBT Plus Placebo (N=18) 13 SD 72,2 Placebo Only (N=18) 13 72,2 **Severity of depressive symptoms at randomisation:** Hamilton Anxiety Rating Scale Escitalopram Plus CBT (N=18) 21.7 SD 3.4 Escitalopram Only (N=19) 21.7 SD 3.6 CBT Plus Placebo (N=18) 54.4 SD 11.7 Placebo Only (N=18) 57.7 12.7 **Inclusion criteria**

	Patients with comorbid unipolar major depression or other anxiety disorders were included only if generalized anxiety disorder was the principal diagnosis Those with a history of substance abuse or dependence were included only if they had been in full remission for at least 6 months. **Exclusion criteria** lifetime history of psychosis or bipolar disorder; cognitive impairment, as determined by a Mini-Mental State Examination (20) score ≤25; current suicidal ideation; ongoing psychotherapy; and medical instability.
Interventions	participants were eligible to be randomly assigned to one of four conditions 1) 16 weeks of escitalopram augmented with 16 sessions of CBT (augmentation phase), followed by 28 weeks of continued escitalopram (maintenance phase) 2) 16 weeks of escitalopram without CBT, followed by 28 weeks of continued escitalopram (maintenance phase) 3) 16 weeks of escitalopram plus CBT, followed by 28 weeks of pill placebo; or 4) 16 weeks of escitalopram without CBT, followed by 28 weeks of pill placebo Tapered according to the following schedule: 10 mg/day every 2 weeks, 5 mg/day every 2 weeks, 2.5 mg/day every 2 weeks, and then placebo for the duration of the maintenance period (or until relapse) cointervention: cognitive-behavioral therapy (CBT)
Outcomes	1- primary Outcomes were anxiety, as measured by the HAM-A, and pathological worry, as assessed with the Penn State Worry Questionnaire (22). The HAM-A is a 14-item interview-rated measure of anxiety primarily assessing somatic symptoms. Participants completed the HAM-A every 4 weeks during the augmentation phase and every 2 weeks during the maintenance phase. The Penn State Worry Questionnaire (22), a 16-item self-report questionnaire measuring excessive and uncontrollable worry, was administered at the beginning and end of the augmentation and maintenance phases. We examined the augmentation effect of CBT on cumulative treatment response, defined two ways based on previous research as follows: achieving a HAM-A score ≤10 (24) and experiencing a decrease ≥8.5 points on the Penn State Worry Questionnaire We also examined improvement in anxiety and worry symptoms using linear mixed models. We modeled the treatment-by-time interaction over the augmentation phase for each outcome separately. Each model included the week 12 HAM-A or Penn State Worry Questionnaire score to control for baseline anxiety or worry severity at the time of randomization, time (weeks), treatment condition (CBT versus no CBT), and the time-by-treatment condition interaction 2- secondary outcome Relapse was defined as two consecutive assessments of 1) a HAM-A score at least 5 points greater than the lowest

	score achieved during the augmentation phase, to a total ≥14, and 2) meeting DSM-IV criteria for generalized anxiety disorder (except the duration criteria). Additionally, onset of a major depressive episode was considered relapse regardless of the participant's HAM-A score
Notes	funding:not report conflict of interest:

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	A statistician created the randomization schedule, and the research pharmacy at each participating institution assigned individuals to conditions in the order of enrollment
Allocation concealment (selection bias)	Unclear risk	not enough information provided
Blinding of participants and personnel (performance bias)	Unclear risk	not enough information provided
Blinding of outcome assessment (detection bias)	High risk	lack of a global outcome measure, such as the Clinical Global Impression improvement rating; and the fact that participants were only followed for 7 months during the maintenance phase
Incomplete outcome data (attrition bias)	Low risk	(95%) randomly assigned participants completed the entire 13-month protocol.All missing data accounted for and reasons for dropouts reported
Selective reporting (reporting bias)	High risk	Comment: the study report fails to include results for adverse events and with- drawal symptoms that would be expected to have been reported for such a study
Other bias	Unclear risk	Limitations of our study are the small sample size; lack of an active control condition for CBT; lack of a global outcome measure, such as the Clinical Global Impression improvement rating; and the fact that participants were only followed for 7 months during the maintenance phase

Zajecka 1998

Methods	**Design:** a randomized, double-blind, placebo-controlled study. **Prerandomisation phase:** Open label fase 12 week and then randomize to placebo and fluoxetine with follow up for 6weeks **Duration post randomisation:** 6 weeks **Aim**: this study analyzed the effects of abrupt fluoxetine discontinuation during a randomized, double-blind, placebo-controlled study of depression maintenance treatment.
Participants	**Country:** nor report

	Setting: not report **Type of AD**:fluoxetine **Duration of antidepressant treatment prerandomisation**:12 weeks **Duration of antidepressant treatment post stabilisation**: 6 weeks **Number of participants:** not clear **Total numbers of randomised participants**: 395 responders were abruptly randomized to placebo (N = 96) or to continued fluoxetine (N = 299). **Primary diagnosis**: depression **Gender distribution :** not report **Mean age, years:** 40 +/- 10 years Severity of depressive symptoms at randomisation: Improvement was defined as a HAM-D-17 score <or= to 7 after 12 weeks of acute treatment with fluoxetine 20 mg dail **Inclusion criteria:** not report **Exclusion criteria:** not report
Interventions	fluoxetine versus placebo Intervention 1: no tapering starting placebo immediatly . Intervention 2: continuation of the same dose of active medication
Outcomes	1- Frequencies and new and worsened adverse events in patients randomized to placebo or to continued fluoxetine treatmentat Patients were seen at weeks 1, 2, 4, and 6 after randomization. Reports of new or worsened adverse events were similar for both groups at each visit after randomization 2- Adverse event data were gathered and catalogued systematically and at regular, specified intervals, and patients were followed up for a sufficiently long period that any discontinuation-related events would be expected to be observed.
Notes	funding: not report conflict of interest: Several factors potentially limit the interpretation of these data. Patients were not treated with more than 20 mg of fluoxetine daily, and it is possible that higher doses could cause problems upon abrupt discontinuation. it is also possible that a 12-week treatment period is too short to predispose patients to problems upon abrupt discontinuation. The nature of discontinuation syndromes related to SSRI use is uncertain, and no specific instrument to measure discontinuation-related signs and symptoms was used. Thus, a very diverse syndrome in which each patient experienced different symptoms could potentially have gone unnoticed

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	insufficient information to judge about the sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: not reported
Blinding of participants and personnel (performance bias)	Low risk	the group whose fluoxetine treatment was discontinued had been randomly selected, and both patients and treaters were blind to treatment condition
Blinding of outcome assessment (detection bias)	Low risk	Adverse event data were gathered and catalogued systematically and at regular, specified intervals, and patients were followed up for a sufficiently long period that any discontinuation-related events would be expected to be observed.
Incomplete outcome data (attrition bias)	High risk	Meer than 20 % missiçng Of the patients switched to placebo, 37 (39%) discontinued because of lack of efficacy and 2 (2%) because of adverse events. In the fluoxetine- treated group, 51 patients (17%) discontinued because of lack of efficacy and 6 (2%) because of adverse events.
Selective reporting (reporting bias)	High risk	the study protocol is available. Most predefined primary and sec- ondary outcomes were reported in a predefined way. Withdrawal symptoms were not reported
Other bias	Unclear risk	Source of funding not reported other bias: patients were not treated with more than 20 mg of fluoxetine daily, and it is possible that higher doses could cause problems upon abrupt discontinuation

- **Characteristics of excluded studies**

Baldwin 2006

Reason for exclusion	participants did not meet the criteria of long-term antidepressants (duration < 3 months) No information over remission vs relapse and total duration of study is 12 weeks

Bockting 2005

Reason for exclusion	compares role of Cognitive therapy in prevention of relapse. No placebo group without medication.

Bockting 2006

Reason for exclusion	compares role of Cognitive therapy in prevention of relapse. No placebo group without medication

Bockting 2008

Reason for exclusion	wrong study design (follow up study)

Bockting 2009

Reason for exclusion	compares role of Cognitive therapy in prevention of relapse. No placebo group without medication

Caillard 2003

Reason for exclusion	No acute treatment phase. this is randomised two-phase study with a total duration of 20 months. Phase I was a 2-month, single-blind placebo period

Cohen 2006

Reason for exclusion	acute treatment phase less than 12 weeks. study was not a randomised discontinuation trial

Coppen 1978

Reason for exclusion	participants did not meet the criteria of long-term antidepressants (duration of open label therapy with AD not reported)

Croft 2002

Reason for exclusion	participants did not meet the criteria of long-term antidepressants (duration < 3 months)

Curtis 1993

Reason for exclusion	participants did not meet the criteria of long-term antidepressants (duration < 3 months)

Davidson 2001

Reason for exclusion	participants did not meet the criteria of long-term antidepressants prescribed for depressive or anxiety disorder study compares effect of sertraline on PTSD not on panic disorders/depression

Davidson 2005

Reason for exclusion	participants did not meet the criteria of long-term antidepressants prescribed for depressive or anxiety disorder study compares effect of sertraline on PTSD not on panic disorders/depression

Davidson 2005a

Reason for exclusion	participants did not meet the criteria of long-term antidepressants and there is no control intervention.

Dobson 2008

Reason for exclusion	placebo group never received AD

Doogan 1992

Reason for exclusion	participants did not meet the criteria of long-term antidepressants (duration < 3 months)

Dubo; 1993

Reason for exclusion	no placebo group

Fava 1994

Reason for exclusion	In both subgroups, antidepressant drugs were tapered and discontinued.(no placebo without drugs overall effect of CBT was monitored)

Fava 1998

Reason for exclusion	In both subgroups, antidepressant drugs were tapered and discontinued.(no placebo without drugs overall effect of CBT was monitored)

GlaxoSmithKline 1994

Reason for exclusion	The study is not found

GlaxoSmithKline 1999

Reason for exclusion	The study is not found

Glen 1984

Reason for exclusion	Open label period is indeed unknown, so exclusion due to unreported duration of pre randomisation phase.

Godfrin 2010

Reason for exclusion	Compare MBCT+ TAU with TAU alone MBCT: mindfulness-based cognitive therapy TAU: treatment as usual (psychotherapy, pharmacotherapy, or combined treatment)

Goodwin 2009

Reason for exclusion	open-label period of 8-10 weeks participants did not meet the criteria of long-term antidepressants (duration < 3 months)

Goodwin 2013

Reason for exclusion	open-label period of study 1 is 8 weeks, study 2 is 8-10 weeks participants did not meet the criteria of long-term antidepressants (duration < 3 months)

Kamijima 2005

Reason for exclusion	Open-label period of 8 weeks. participants did not meet the criteria of long-term antidepressants (duration < 3 months)

Kamijima 2006

Reason for exclusion	Open-label period of 8 weeks. participants did not meet the criteria of long-term antidepressants (duration < 3 months)

Klerman 1974

Reason for exclusion	Amitriptyline and little psychotherapy compared to psychotherapy without medication.

Lepine 2004

Reason for exclusion	Not included due to only 2 months of placebo The study includes two phases: Phase 1: (two months) single-blind placebo period to determine remission. Phase 2: (18 months) double-blind phase with sertraline or placebo.

Licht 2013

Reason for exclusion	Not included, because placebo period of 1 month for everyone

Liebowitz 1999

Reason for exclusion	Exclusion because no randomisation and treatment with phenelzine lasts longer than 6 months

Liebowitzb2010

Reason for exclusion	intervention was not discontinuation of antidepressants (quetiapine)

Markowitz 2000

Reason for exclusion	Open-label phase is 8 weeks. participants did not meet the criteria of long-term antidepressants (duration < 3 months)

Michelson 1999

Reason for exclusion	Open-label phase is 10 weeks. participants did not meet the criteria of long-term antidepressants (duration < 3 months)

Montgomery 1993 a

Reason for exclusion	participants did not meet the criteria of long-term antidepressants (duration < 3 months)

Montgomery 1993

Reason for exclusion	participants did not meet the criteria of long-term antidepressants (duration < 3 months)

NCT00878748

Reason for exclusion	Ful article was not found. Based on abstract exclusion and not verifiable in full text

OADIG 1993

Reason for exclusion	Participants did not meet the criteria of long-term antidepressants (duration < 3 months)

rapoport 2010

Reason for exclusion	This study examines whether continuation therapy with citalopram can prevent a relapse following remission of major depression due to traumatic brain injury.

Reynolds 1992

Reason for exclusion	Study is not a controlled study

Reynolds 1999

Reason for exclusion	Not all participants met the criteria for long-term antidepressants (the median duration of acute treatment for the 61 patients who completed treatment was 9.1 weeks)

Rosenbaum 1998

Reason for exclusion	Participants did not meet the criteria for long-term antidepressants (duration open-label fluoxetine, sertraline, or paroxetine for 4–24 month)

Sackeim 2001

Reason for exclusion	Study is excluded due to patients having electroconvulsive treatment before randomisation

Schmidt 2002

Reason for exclusion	Participants did not meet the criteria for long-term antidepressants (No placebo group)

Shawyer 2012

Reason for exclusion	Participants did not meet the criteria for long-term antidepressants (participants without antidepressant treatment)

Shimazu 2011

Reason for exclusion	intervention is not discontinuation of antidepressant treatment of antidepressant treatment

shimodera 2012

Reason for exclusion	intervention is not discontinuation of antidepressant treatment of antidepressant treatment

stein 1996

Reason for exclusion	open label study less than 12 weeks

Stocchi 2003

Reason for exclusion	participants did not meet the criteria of long-term antidepressants (duration < 3 months)

Teasdale 2000

Reason for exclusion	participants did not meet the criteria of long-term antidepressants (off antidepressant treatment)

Tint 2008

Reason for exclusion	No comparator control intervention, no placebo

Weissman 1976

Reason for exclusion	wrong study design (follow up study)

Wentink 2019

Reason for exclusion	No comparator control intervention

10. Personal reflections (in dutch):

Persoonlijke reflectie Aman Omar:

Drie jaar geleden besloten Sarah, Mina en ik om samen onze masterproef te maken. We kenden elkaar al van tijdens onze opleiding geneeskunde aan de Universiteit Gent. We waren goede vriendinnen. Het bijzondere was dat we alle drie onze diploma's in de geneeskunde buiten België hadden behaald en hier opnieuw moesten studeren voor de master in de geneeskunde. Dat betekende ook dat we eerst Nederlands moesten leren.

Ik wist dan ook dat Sarah en Mina harde, stipte werker waren, mensen waarmee ik deze thesis wel goed zag komen. Gelukkig dachten zij er hetzelfde over. Samenwerken met zulke toegewijde en betrouwbare vriendinnen gaf me de motivatie en het enthousiasme om ons project aan te pakken.

De afgelopen drie jaar zijn naar mijn mening goed verlopen. Sarah, Mina en ik hebben verschillende kwaliteiten, wat ervoor zorgde dat elk aspect van de masterproef door één van ons werd opgenomen.

Wij zijn allemaal geïnteresseerd in literatuuronderzoek. Daarom hebben we gekozen voor een onderwerp over het stoppen van antidepressiva (AD) bij personen met AD voor angst of depressie die stabiel zijn en waarbij de duur van de AD minder dan 6 maand was, omdat we merkten dat veel mensen in België AD langdurig gebruiken en het niet duidelijk is wanneer artsen ermee moeten stoppen. We denken allemaal dat het heel belangrijk onderwerp is.

Zo kwamen we in contact met onze promotor, prof. dr. Thierry Christiaens van de U Gent en met dr. Ellen Van Leeuwen, onze co-promotor.

Het gesprek met onze promotor en co-promotor verliep online, via Microsoft-team.

Het doel van onze review (met meta-analyse) is om te kijken naar de studies waarin antidepressiva (AD) werden stopgezet bij patiënten met (stabiele) depressie of angst, waarbij de behandeling met AD korter dan 6 maanden heeft geduurd, en om dit te vergelijken met het voortzetten van de AD-behandeling.

De onderzoeksvraag is: wat is de haalbaarheid en veiligheid hiervan?

Het is zeer belangrijk om bij het literatuuronderzoek een strikte methodologie te volgen, onze co-promotor heeft ons hierbij geholpen. Ze stond altijd klaar om onze vragen te beantwoorden. Allereerst kregen we van haar een lijst van 78 studies. Gelukkig waren de meeste van deze studies beschikbaar in PubMed, waartoe we toegang hadden via Athena van de Universiteit Gent. Vervolgens moesten we de studies die voldeden aan de criteria selecteren.

Het selectieproces verliep soms op basis van het lezen van de abstract, waarbij we konden beslissen of de studie aan onze criteria voldeed en kon worden opgenomen. In andere gevallen was het nodig om het volledige artikel te lezen om een definitieve beslissing te nemen. Op basis daarvan hebben we 26 artikelen geselecteerd.

Voor elke studie moesten we een beschrijving en risk of bias opstellen, waarbij we een specifieke sjabloon voor elke studie apart invulden. We hebben een online cursus gevolgd over systematische review en meta-analyse om dit goed te begrijpen.

Dus in het eerste jaar van onze opleiding hebben we alle sjablonen en risk of bias-beoordelingen ingevuld.

Tijdens het tweede jaar hebben we alle onderzoeksgegevens, waaronder ongewenste effecten, levenskwaliteit, depressieve symptomen, angstsymptomen en ontwenningsverschijnselen, in het computerprogramma Review Manager (RevMan) ingevoerd.

RevMan is inderdaad een software die wordt gebruikt voor het voorbereiden en bijhouden van Cochrane-reviews. Om efficiënt met dit programma te kunnen werken, hebben we ook online cursussen gevolgd.

In het derde jaar hebben we de resultaten samengevoegd en de analyses uitgevoerd. Nadat we klaar waren met het interpreteren van de resultaten, hebben we de discussie en conclusie geschreven.

Om resultaten te interpreteren hebben we forest plot gebruiken. Forest plot is een grafische weergave van de resultaten van verschillende studies die in een meta-analyse zijn geïncludeerd.

We hebben de review van onze co-promotor als voorbeeld gebruikt.
Zij en haar collega's hebben een review met meta-analyse uitgevoerd over het stoppen van antidepressiva bij patiënten met angst of depressie die stabiel waren en waarbij de duur van de AD-behandeling langer dan 6 maanden was.
Samengevat geven de studies van onze thesis onvoldoende bewijs om te suggereren dat het stoppen van antidepressiva veilig en effectief is in vergelijking met voortzetten na remissie bij personen die antidepressiva gedurende een periode van 3 tot 6 maanden hebben gebruikt.
We werkten stap voor stap, waarbij we bij elke stap met elkaar overlegden, en de taken onderling verdeelden. Elk meningsverschil losten we op in overleg.
Bij elke stap werden we gevolgd door onze co-promotor. De overleg met haar vond maandelijks plaats via Microsoft-team, maar ze was altijd klaar om onze vragen te antwoorden.
We waren het erover eens dat één van ons een bepaald stuk zou schrijven en de andere twee het zouden controleren. Soms schrijven we samen een bepaald stuk.
Het uitvoeren van deze thesis vroeg tijd en energie, maar de samenwerking tussen ons was geweldig. We zijn heel blij dat we dit werk hebben kunnen uitvoeren.
Ik vind dat het onderwerp van onze masterproef van groot belang is voor elke huisarts. Hoewel er geen duidelijk antwoord op onze vraag is.

Persoonlijke reflectie Mina Al-Saad:

Een masterproef beginnen, voortzetten en afwerken is een intens, verrijkend, interessant, maar soms ook uitputtend proces. Het is een intensief traject waarin de uiteindelijke resultaat is tot stand gekomen dankzij de hulp en steun van velen.Vanwege de omvang en aard van het onderzoek werd deze masterproef uitgewerkt door 3 studenten: Sarah, Aman en ik. We hebben elkaar leren kennen toen we terug geneeskunde studeerden aan de Universiteit Gent. Als buitenlandse studenten deelden we dezelfde situatie en hetzelfde doel. We hebben elkaar ondersteund en aangemoedigd tijdens het studieproces en bij het tot stand brengen van dit eindwerk.

Toen ik het onderwerp moest kiezen voor de masterproef, heb ik zonder twijfel gekozen voor deze onderwerp: Effect en veiligheid van stoppen versus continu gebruik van antidepressiva bij depressie/angst (literatuuronderzoek).
Nadat we contact hadden opgenomen met onze promotor Prof. dr. Thierry Christiaens en onze co-promotor Dr. Ellen van Leeuwen, kregen we de gelegenheid om deze masterproef uit te schrijven.

Vanuit mijn persoonlijke interesse, alsook de relevantie van dit onderwerp in de huidige patiëntenpopulatie werd dan ook gekozen om mijn masterproef te maken rond ‘effectiviteit en veiligheid van anti depressieva te stoppen versus het voortzetten van langdurig antidepressiva gebruik.
Je hoort het in de media, zie het in de praktijk en leest het in de literatuur: er is een stijgend gebruik van antidepressiva; vooral van het langdurig gebruik van deze medicatie. Mede door de coronacrisis zijn er meer mensen met depressie en /of angst. Volgens sciensano, vertoonde in totaal 24% van de Belgische bevolking angst of een depressieve stoornis.

Net als de meeste medicijnen kunnen antidepressiva bijwerkingen en nadelige effecten hebben. Diverse richtlijnen adviseren om antidepressiva gedurende een bepaalde periode na remissie te blijven gebruiken, maar variëren in de aanbevolen periode. Er is veel aandacht besteed aan het wel of niet starten en opbouwen van antidepressiva, maar op dit moment is er te weinig overtuigend bewijs voor betrouwbare voorspellers van wanneer en hoe mag worden afgebouwd of gestopt met antidepressiva.

Het doel van deze review was het beoordelen van de effectiviteit en veiligheid van antidepressieva te stoppen versus het voortzetten van langdurig antidepressiva gebruik.
Deze masterproef is een literatuuronderzoek waardoor de verzameling van 78 studies werden door de hulp van onze co-promotor gekozen. We hebben deze studies verdeeld met ons drie en gingen we op zoek naar gepaste artikels die de juiste informatie bevatten voor ons onderzoek.

In eerste instantie hebben we met behulp van een specifiek sjabloon voor elke studie een studie karakteristiek en de risk of biaas opgesteld.
We hebben de resultaten van deze meta-analyses met behulp van Cochrane Review uitgevoerd. We hebben samen het gedeelte met de resultaten, discussie en conclusie opgeschreven. Voor elke stap hebben we elkaars werk gecontroleerd. Voor de correctie van het Engels heeft sarah meer gefocust maar hebben we ook hulp gekregen van Dr. Leeuwen en prof. Christiaens.

Wanneer we vragen hadden of iets onduidelijk was, hebben we contact opgenomen met onze co-promotor Dr. Ellen van leeuwn.

Omwille van de grote afstand, ik woon zelf in Hasselt, Aman in Antwerpen en Sarah in Gent, waren onze meetings altijd online. We kwamen online zeer regelmatig samen, vaak om de twee weken om te bespreken over ons thesis, informatie uit te wisselen en ons taken te verdelen.

Het verkrijgen van feedback van onze promotoren verliep steeds vlot. De regelmatige online meetings met onze copromotor hielp bij het voltooien van deze masterproef.

Tenslotte:het stoppen met antidepressiva is een belangrijk onderwerp voor de honderdduizenden patiënten die elk jaar (willen) stoppen, maar ook voor artsen en apothekers. Robuust wetenschappelijk bewijs ontbreekt grotendeels, met als gevolg dat de discussie over het stoppen van antidepressiva te weinig op basis van wetenschappelijk bewijs wordt gevoerd. Om de puzzel van het stoppen met antidepressiva op te lossen, is het essentieel om de incidentie van terugval en ADS beter in kaart te brengen. Maar ook om de onderliggende mechanismen van terugval en ADS te begrijpen en met gerandomiseerd en geblindeerd onderzoek te onderbouwen welke afbouwstrategieën het meest effectief zijn, waarmee ADS en terugval te minimaliseren zijn. Deze kennis is nodig om een antidepressivum zo veilig en rationeel mogelijk af te bouwen en ‘afbouwangst’ bij de behandelaar of de patiënt te voorkomen. De klinisch relevante vragen waar antwoorden
voor nodig zijn, zijn de volgende:
1- op welk moment na remissie kan/moet iemand stoppen?
2- welke individuele kenmerken zijn bepalend voor ADS en/of het terugvalrisico na stoppen?
3- welke rol spelen anticipatie effecten bij het stoppen?
4-met welke snelheid en doseringsstappen kan iemand succesvol afbouwen?

Conclusie
Afbouwen en stoppen met antidepressiva is een belangrijk onderwerp waarvoor terecht steeds meer aandacht is. Direct bij de start van een antidepressivum dient het onderwerp besproken te worden door arts en apotheker. Goede informatie en gezamenlijke besluitvorming kunnen ervoor zorgen dat iemand goed kan besluiten om wel of niet te stoppen, maar ook wanneer en hoe. Zowel bij de voorlichting als tijdens het afbouwproces staan de patiënt en diens naasten centraal, maar dienen psychiater, huisarts en apotheker ook samen te werken, ondersteund door bestaande en waardevolle initiatieven van patiëntenverenigingen .

Persoonlijke reflectie Mustafa Sarah:

Ik was eerst afgestudeerd als basisarts in Pakistan en ben naar België gekomen in 2015 en woon in hier al 8 jaar. Mijn diploma uit Pakistan werd hier erkend als bachelor in de geneeskunde. Daarom deed ik een master in geneeskunde aan de Universiteit Gent (het 3 jaar programma van 2017-2020. 2020 was een heel bijzonder jaar geweest voor mij. Ik was begonnen met mijn stage als HAIO in het wijkgezondheid centrum Brugse poort. In het WGC heb ik de mogelijkheid gehad om patiënten met verschillende achtergronden en met psychiatrische klachten op te volgen. Ik zag minimum 3-4 patiënten per week die antidepressiva gebruiken als chronische medicatie daarom wou ik een onderwerp kiezen over antidepressiva voor mijn masterproef. Drie jaar geleden hebben Mina, Aman en ik besloten om samen onze masterproef te maken over antidepressiva door onze gemeenschappelijke interesse in het onderwerp. We kennen elkaar reeds van de master opleiding in Ugent. We gingen op zoek naar een onderzoeksonderwerp dat ons haalbaar leek om in 3 jaar te kunnen voltooien. Zo kwamen we in contact bij het literatuuronderzoek, een voorstel van onze promotor Prof.dr. Thierry Christiaens en onze co-promotor Dr Ellen van Leeuwen, met het onderwerp : Effect en veiligheid van stoppen versus continue inname van antidepressiva bij depressie/angst (literatuuronderzoek) via website van ICHO.
Ons co-promotor Dr E. van Leeuwen had een review met meta-analyse gedaan van alle RCTs die antidepressiva (AD) stoppen bij personen met AD voor angst of depressie die stabiel zijn en waarbij de duur van de AD meer dan 6 maand was. In haar review was er geen duidelijk antwoord op de vraag of het haalbaar en veilig is en wat het effect is van stoppen van AD. Daarom wilden we dit verder onderzoeken. Het doel van de nieuwe review (met meta-analyse) is om te kijken naar de studies die AD stoppen bij personen met (stabiele) depressie of angst waarbij AD korter dan 6 maand gegeven werd versus het blijven doorgeven van AD met als onderzoeksvraag: wat is de haalbaarheid en de veiligheid van stoppen van AD minder dan zes maand bij personen met depressie of angst die stabiel zijn versus het doorgeven van AD?

We startten onze thesis met een oriënterend online cursus voor systematische review en meta-analyse via https://www.coursera.org/learn/systematic-review op aanraden van ons co promotor. We gingen aan de slag met het leren invullen van een sjabloon ter beschrijving van studies en risk of bias opstellen. Het sjabloon hadden wij gedownload van https://training.cochrane.org/data-collection-form-rcts.Invullen.

Risk of bias hebben wij geleerd via:https://training.cochrane.org/handbook/current/chapter-08#section-8-1.

Bij vragen en onduidelijkheden hebben wij contact opgenomen met onze co-promotor.
De studies moeten wij niet zelf zoeken via een literatuur search .Wij hadden 78 studies gekregen door onze co-promotor Dr Ellen van Leeuwen . Nadien gingen we aan de slag met de selectie van studies voor inclusie en wij hebben 26 studies geïncludeerd om deze review te schrijven. Nadien hebben wij deze 26 studies onderling verdeeld om een beschrijving van de studies weer te geven en een risk of bias op te stellen. Ik heb de beschrijving gedaan voor 9 studies, Mina 8 studies en ,Aman 9 studies. Elke stap hebben wij per twee gecontroleerd. Onenigheid losten wij op door middel van discussie en overleg met Dr Ellen van Leeuwen.
Wij hebben voor elke studie een beschrijving van de studies en risk of bias opgesteld , alle onderzoek data ingebracht in het computerprogramma Revman , vervolgens hebben wij resultaten samengenomen , analysen gedaan per uitkomst en de resultaten geïnterpreteerd om onze discussie en conclusies te schrijven .

Mina en ik hebben gefocust op Het schrijven van de inleiding en Aman heeft dit ook gecontroleerd en aangevuld waar nodig. Aman en ik hebben verder gefocust op het uitschrijven van Abstract,methodologie en discussie en Mina heeft dit later gecontroleerd en aangevuld waar nodig.

Het gedeelte met de resultaten ,risk of bias ,interpretatie van resultaten hebben we samen uitgeschreven.
Voor juiste interpretatie van data en analysen heeft onze co promotor dr E. van Leeuwen ons altijd geholpen. Op die manier konden we onze resultaten en discussie uitschrijven. Het verkrijgen van feedback van onze co-promotor verliep steeds vlot.
Tussen de verschillende deadlines in, hebben Mina, Aman en ik elkaars geschreven teksten in het thesisdocument nagelezen, verbeterd en aangevuld. We hebben elk op andere momenten doorheen het jaar meer of minder werk gehad, maar in het algemeen hebben we alle drie evenveel werk en tijd in deze thesis gestoken.
Elke stap heeft veel tijd en energie gevraagd. In de totaliteit van dit onderzoek waren er soms problemen in de samenwerking en wij konden niet altijd op hetzelfde tempo werken door verschillende persoonlijke en praktische redenen. Daarom was het niet gelukt om onze masterproef af te ronden en in te dienen tijdens de eerste zittijd en wij Hebben besloten om onze masterproef in te dienen in de tweede zittijd .
Maar overal vormden wij een goed team met heldere communicatie en duidelijke afspraken en deadlines. We overlegden regelmatig via Microsoft-teams met elkaar en onze co-promotor Dr van Leeuwen en zo is het gelukt om deze thesis samen te schrijven.

Persoonlijke visie op consequenties voor het werkveld :
De reden achter de keuze voor dit onderwerp is voor mij, als huisarts, dat dit een heel belangrijke klinische vraag blijft, hoelang antidepressiva mogen gegeven worden na remissie. Wat is haalbaarheid en hoelang kan en mag antidepressiva worden gegeven en hoe bouw je dit af om een succesvolle behandeling na te streven.
Huidige richtlijnen aanbevolen om antidepressiva af te bouwen om relapse /recurrence te vermijden, raden een acuut stoppen met een antidepressivum af, omdat dit tot onttrekkingsverschijnselen kan leiden (NHG 2022)
Deze review (met meta-analyse) biedt onvoldoende bewijs om te suggereren dat stoppen en zeker abrupt stoppen van antidepressiva veilig en effectief is in vergelijking met voortzetten na remissie bij personen die antidepressiva hebben gebruikt gedurende een periode van 3 tot 6 maanden. Deze review biedt geen informatie over de rol van shared descion making en tapering van antidepressiva, de culturele context, de persoonlijke draagkracht van de patiënt, de omstandigheden en de psychosociale behandelingen over de mogelijke rol in het afbouwen en stoppen van antidepressivum na een succesvolle behandeling. Toekomstig onderzoek zal zich moeten richten op het bestuderen van verschillende afbouwstrategieën en hoe psychologische benaderingen en shared decision making kunnen helpen om recidive depressie te voorkomen.

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