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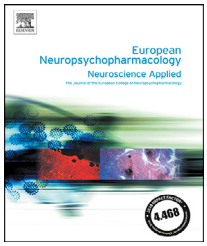

REVIEW

Efficacy and tolerability of pharmacological and non-pharmacological interventions in older patients with major depressive disorder: A systematic review, pairwise and network meta-analysis

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Abstract
As there is currently no comprehensive evaluation about the efficacy and safety of interventions in elderly patients with major depressive disorder, we did a systematic review and network meta-analysis about all interventions in this population.
We searched the specialised register of the Cochrane common mental disorders group, MEDLINE, EMBASE, PsycINFO, CochraneLibrary, ClinicalTrials.gov and the WHO registry until Dec 12, 2017 to identify all randomized controlled trials about the treatment of major depressive disorder in patients over an age of 65. The primary outcome was response defined as reduction of at

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least 50% on the Hamilton Depression Scale or any other validated depression scale. Secondary outcomes were remission, depressive symptoms, dropouts total, dropouts owing to inefficacy and dropouts due to adverse events, quality of life and social functioning. Additionally, we analysed 116 adverse events.
We identified 129 references from 53 RCTs with 9274 participants published from 1990 to 2017. The mean participant age was 73.7 years. In terms of the primary outcome response to treatment the network-meta-analysis showed significant superiority compared to placebo for quetiapine and duloxetine; in addition, agomelatine, imipramine and vortioxetine outperformed placebo in pairwise meta-analyses, and there were also significant superiorities of several antidepressants compared to placebo in secondary efficacy outcomes. Very limited evidence suggests that competitive memory training, geriatric home treatment group and detached mindfulness condition reduce depressive symptoms.
Several antidepressants and quetiapine have been shown to be efficacious in elderly patients with major depressive disorder, but due to the comparably few available data, the results are not robust. Differences in the multiple side-effects analysed should also be considered in drug choice. Although there were significant effects for some non-pharmacological treatments, the overall evidence for non-pharmacological treatments in major depressive disorder is insufficient, because it is based on a few trials with usually small sample sizes.

1. Introduction

Depression is the leading cause of the global burden of disease, and this burden has substantially increased since 1990, largely driven by population growth and ageing (Murray et al., 2015). The prevalence in older patients is estimated between 10 and 20% (Chew-Graham et al., 2004), and it has negative consequences for the afflicted individuals such as poor quality of life, a higher risk for other illnesses, and in extreme cases death by suicide. The highest rates of suicide are seen in those over the age of 75 (Lapierre et al., 2011) and, with the increasing number of seniors, by 2020 suicide is expected to be the tenth most common cause of death in the older population (Lapierre et al., 2011).

Antidepressants are the most frequently used treatment and showed efficacy in the general population compared to placebo (Cipriani et al., 2018). However, there are many compounds which differ in efficacy and side-effects, and which is the "best" antidepressant for older people is still unclear. Due to small effect sizes in meta-analysis in adults (age range 18–65 years) there is also a debate about the efficacy of antidepressants and some authors have claimed that they do more harm than good (Gøtzsche et al., 2015). Beside antidepressants there are other pharmacological options for the treatment of major depressive disorder (MDD), for example certain antipsychotics (Maneeton et al., 2012) or benzodiazepines which have potential (Petty et al., 1995) antidepressant effects. Most of the previous reviews were clearly out of date (> 10 years) (Cuijpers et al., 2006; McCusker et al., 1998; Mittmann et al., 1997; Stek et al., 2003; Williams, 2000; Wilson et al., 2001). Other ones were restricted to a single drug (citalopram (Seitz et al., 2010)), a single psychotherapy (cognitive behavior therapy or reminiscence techniques (Peng et al., 2009)), physical activity only (Bridle et al., 2012). restricted to a single comparison (antidepressants compared to placebo (Wilson et al., 2001) (out of date), a single outcome (severity of depression (Cuijpers et al., 2006) out of date) specific patients such as ambulatory patients (McCusker et al., 1998), out of date) or treatment-resistant patients (Cooper et al., 2011) (10 out of 13 studies are non-randomized trials). Other reviews were restricted to maintenance treatment (Wilkinson and Izmeth, 2012), or were simply narrative systematic reviews, i.e. they did not apply meta-analytic methods (Apostolo et al., 2015; Kiosses et al., 2011; Mura and Carta, 2013). Importantly, with one exception (Thorlund et al., 2015) no systematic review applied network meta-analytic techniques. This single review was restricted to 15 RCTs on selective-serotonin-reuptake inhibitors (SRRIs) and selective-norepinephrine-reuptake inhibitors (SNRIs), it only analysed response and a few safety outcomes. Moreover, a more relaxed age inclusion criterion (≥ 60 years) was applied compared to the current review (≥ 65 years (Thorlund et al., 2015).

Older patients with MDD differ substantially from the adult age group, and such differences should lead into an individual treatment of this sensitive subgroup. Physiological differences include age-related changes which affect pharmacokinetics (Klotz, 2009), high multimorbidity, elevated probability of drug interactions due to polypharmacy (Lotrich and Pollock, 2005), impaired postural control associated with a higher risk of falls (Lotrich and Pollock, 2005), and a higher sensitivity to adverse events (DeVane and Pollock, 1999). Moreover, older patients are confronted with important changes in life such as retirement which can contribute to depression. The other mainstay of treatment are various forms of psychotherapy and psychosocial interventions, but also other non-pharmacological interventions, some of which may be better treatment options for this population. However, their effectiveness for older adults (> 65 years) has not been analysed systematically yet. The current systematic review attempts to fill this gap, by conducting a random effects pairwise- and network-meta-analysis. The aim was to meta-analytically assess all pharmacological and non-pharmacological

interventions studied in terms of efficacy and safety including all available evidence from randomized controlled trials.

2. Experimental procedures

2.1. Participants and interventions

An a priori written study protocol was registered at PROSPERO: CRD42018107814 (Krause et al., 2018) (eAppendix 1). Our analysis aimed to include all RCTs about older patients with an operationalised diagnosis of acute MDD. We included all pharmacological and non-pharmacological interventions with a minimum study duration of 4 weeks. Drugs had to be used as monotherapy. We will provide the dataset on Mendely after publication.

2.2. Search strategy and selection criteria

We did a comprehensive, systematic literature search in the specialised register of the Cochrane common mental disorders group, MEDLINE, EMBASE, PsycINFO, CochraneLibrary, ClinicalTrials.gov and the WHO registry until Dec 12, 2017 (eAppendix 2). Moreover, we inspected the reference lists of the included studies and previous reviews (Cipriani et al., 2018).

To ensure comparability, we excluded studies where all patients had a specific comorbidity per inclusion criteria. Due to the reasons explained in detail in the discussion we defined older patients with a minimum age of 65 years. We excluded studies before 1990 to take into account the placebo response had increased until approximately this time, while it remained stable thereafter (Furukawa et al., 2016; Rutherford and Roose, 2013).

For crossover studies, we only used the first phase to avoid carryover effects (Elbourne et al., 2002). We excluded cluster-randomized trials (Divine et al., 1992). Furthermore, studies that demonstrated a high risk of bias for sequence generation or allocation concealment were excluded (Higgins JPT, 2011). If a trial was described as double-blind but randomization was not explicitly mentioned, we assumed that study participants were randomized. Study quality was independently assessed by at least 2 reviewers (MK, KG) using the Cochrane Collaboration's risk-of-bias tool (Higgins JPT, 2011). We excluded studies from mainland China to avoid a systematic bias because many of these studies do not use appropriate randomization procedures, do not report their methods, and have been reported to be not reliable (Bian et al., 2006; Wu et al., 2009). We sent emails to the first and corresponding authors of all included studies to ask for missing data.

2.3. Outcome measures and data extraction

The primary outcome was the number of patients who responded to treatment, showing a reduction of at least 50% on the Hamilton Depression Scale (HAM-D (HAMILTON, 1960)), Montgomery-Asberg-Depression Scale (MADRS (Montgomery and Asberg, 1979)), Beck Depression Inventory or any other validated depression scale; or "much or very much improved" (score 1 or 2) on CGI-Improvement (Guy, 1976).

Secondary outcomes were number of participants in remission, depressive symptoms at endpoint/mean reduction of depressive symptoms from baseline to endpoint, dropouts owing to any reason (all-cause discontinuation), dropouts owing to inefficacy of treatment and dropouts due to adverse events. Further efficacy outcomes we analysed were quality of life and social functioning. As we expected a broad range of different adverse events in older patients, we analysed all reported side-effects. To classify side-effects we adapted the standardized MedDRA query (Mozzicato, 2007).

Study selection and data extraction were performed independently by at least 2 reviewers (MK, KG). Disagreement was resolved by discussion. If disagreement could not be resolved, we discussed with the team leader (SL) and contacted the authors per e-mail seeking further information. Missing standard deviations were estimated from P values or substituted by the mean SD of the other included studies using the same rating scale.

2.4. Statistical analysis

We performed both random effects pairwise and network meta-analysis in a frequentist framework using Stata 14 (Chaimani and Salanti, 2015; White, 2015; White et al., 2012). For continuous outcomes, we calculated standardized mean differences (SMDs) (Higgins et al., 2012). For binary outcomes, the effect sizes were estimated as risk ratios (RRs). Both types of effect sizes were presented along with their 95% confidence intervals (CIs). We assumed a common heterogeneity value across all comparisons. When sufficient data to estimate the between-study variance were not available, we used the fixed effect model.

We also estimated the relative ranking of the various antidepressants and other interventions based on the surface under the cumulative ranking curves (SUCRA) (Salanti et al., 2011). SUCRA percentages range from 0 to 1, with 1 indicating that a treatment is certain to be the best and 0 that a treatment is certain to be the worst.

Prior to running network meta-analysis, we attempted to assess the transitivity assumption (Cipriani et al., 2013; Jansen and Naci, 2013; Salanti, 2012). This assumption implies that studies comparing different sets of interventions are sufficiently similar to provide valid indirect inferences, which we tried to ensure by applying narrow inclusion criteria and making populations similar within and across treatment comparisons. In the presence of sufficient data, we also considered whether the potential effect modifiers were distributed similarly across the available comparators (eAppendix 8). Important intransitivity might be manifested in the data as statistical inconsistency (disagreements between direct and indirect evidence).

Statistical inconsistency was tested with three different approaches: the loop-specific approach that tests inconsistency in every closed loop of evidence (Bucher et al., 1997); the side-splitting method that tests for each comparison's discrepancies between direct and indirect evidence obtained by the entire network (Dias et al., 2010); and the design-by-treatment interaction model that tests inconsistency from all possible sources in the network jointly (Higgins et al., 2012). The magnitude of inconsistency factors and their respective P values were used to identify the presence of inconsistency. We judged inconsistency in the entire network or loops to be inconsistent with a significant disagreement between direct and indirect evidence ($P < 0.10$).

A priori we planned subgroup and meta-regression analyses for baseline severity, pharmaceutical company sponsorship and allegiance bias (Brunoni et al., 2009), study duration, drug dose or frequency and duration of intervention, degree of placebo response (Furukawa et al., 2016; Walsh et al., 2002) and publication year. Meta-regressions were done in a Bayesian framework and assuming a common regression coefficient across comparisons to increase the power of the analysis.

We assessed potential small-trial effects and publication bias, using simple funnel-plots for pairwise meta-analyses and comparison-adjusted funnel plots for network-meta-analysis, if at least 10 and 3 trials per comparison were available respectively (Chaimani et al., 2013). Additionally, we assessed the confidence in estimates of the primary outcome with Confidence in Network Meta-Analysis (CINeMA) (CINeMA, 2017; Salanti et al., 2014), an

adaptation of the Grading of Recommendations Assessment, Development and Evaluation framework (GRADE) specifically developed for network meta-analysis (Salanti et al., 2014).

3. Results

3.1. Description of included studies

We identified 129 references from 53 (46 included usable outcome data) RCTs with 9274 participants published from 1990 to 2017. The PRISMA flowchart is shown in Fig. 1 and details of all included studies in Table 1. Of 8514 patients with gender indicated, 5820 were woman (68%). The mean age of participants was 73.7 years with a range of 68.9 - 83.2; the mean duration of illness was 9.08 years. The mean trial duration was 9 weeks. The assessment for risk of bias is presented in eAppendix4 in the Supplement. Antidepressants were the most studied intervention (44 of 53 included trials), followed by eight studies about non-pharmacological interventions and one placebo-controlled quetiapine study (Katila et al., 2013) (Table 1). The mean dose of the 17 antidepressants included in the analysis was 30.20 mg/d in fluoxetine equivalents. Fig. 2 shows the network of eligible comparisons for the primary outcome. It should be noted that non-pharmacological RCTs were not connected to the drug network and were therefore analysed separately. Network plots for secondary outcomes are presented in eAppendix5. Due to the limited word count we will generally present only the results of the network-meta-analysis, except for outcomes where a network-meta-analysis was not possible or where inconsistency was high (response to treatment and depressive symptoms, see below). Other pairwise meta-analyses are shown in eAppendix 7.

3.2. Response

The results of NMA for the primary outcome, response defined as a reduction of at least 50% in depressive symptoms are summarized in Fig. 3. Quetiapine and duloxetine showed significantly higher response rates compared to placebo (mean RR 2.09 and RR 1.83). They were also associated with significantly higher response rates compared to escitalopram, venlafaxine, citalopram, clomipramine, mianserin, trazodone, fluoxetine, tianeptine, nortriptyline and maprotiline (range of mean RRs for quetiapine: 2.00–3.84; range of mean RRs for duloxetine: 1.76–3.37). The four last mentioned drugs were associated with significantly lower response rates compared to several other drugs (Fig. 3). Drugs are reported in order of their individual SUCRA-ranking, which should be interpreted carefully because the precision of effects is low for most of the comparisons and because there was significant inconsistency (see paragraph Consistency of the network below). The results of pairwise meta-analysis are shown in the supplement eAppendix 7. Agomelatine, duloxetine, imipramine, quetiapine and vortioxetine were associated with higher response rates compared to placebo (RRs 1.53, 1.81, 1.71, 2.09, 1.49).

95% confidence intervals for the results of this and all other outcomes are presented in the respective tables due to space limitations.

3.3. Remission

Quetiapine, mirtazapine and duloxetine were associated with significantly more patients in remission compared to placebo (mean RRs 2.38, 1.90, 1.52). In terms of comparisons between drugs quetiapine was associated with significantly more frequent remission compared to duloxetine, vortioxetine, sertraline, citalopram, amitriptyline, bupropion, escitalopram, nortriptyline, venlafaxine, fluoxetine and tianeptine (RRs 1.57, 1.76, 2.00, 2.01, 2.03, 2.09, 2.50, 2.84, 2.91, 3.27, 5.68). Venlafaxine, fluoxetine and tianeptine were associated with significantly lower remission rates compared to many other drugs (Fig. 3).

3.4. Depressive symptoms

In NMA, only escitalopram showed significant higher reduction of depressive symptoms compared to placebo (mean SMD −0.81) (eTab1). Inconsistency was significant (see consistency of the network below). In pairwise meta-analyses agomelatine, duloxetine, escitalopram, imipramine, quetiapine, tianeptine and vortioxetine were associated with higher reduction of depressive symptoms in comparison to placebo (SMD's −0.36, −0.38, −1.08, −0.52, −0.88, −0.54 and −0.36) (eAppendix7).

3.5. Total dropouts

Fluoxetine and amitriptyline were associated with significantly more dropouts compared to placebo (mean RRs 1.49 and 1.81). Agomelatine showed significantly fewer dropouts compared to citalopram, paroxetine, fluoxetine, mianserin, sertraline, venlafaxine, fluvoxamine, amitriptyline, nortriptyline, maprotiline, lofepramine. Furthermore there were significantly more dropouts in duloxetine treated patients compared to amitriptyline (RR 1.94) (eTab2).

3.6. Dropouts due to inefficacy

Quetiapine and duloxetine were associated with significantly fewer dropouts due to inefficacy compared to placebo (mean RRs 0.09, 0.25) and bupropion (RRs 0.08, 0.23) (eTab3).

3.7. Dropouts due to adverse events

Duloxetine, escitalopram, sertraline, fluoxetine, paroxetine, quetiapine, amitriptyline, mianserin, venlafaxine and nortriptyline were associated with significantly more dropouts due to adverse events compared to placebo (mean RRs 1.68, 2.07, 2.22, 2.53, 2.62, 2.76, 2.81, 3.05, 3.27, 3.68) and bupropion (RRs 2.22, 2.73, 2.93, 3.34, 3.46, 3.64, 3.71, 4.03, 4.05, 4.86). (eTab4).

3.8. Quality of life and social functioning

Quetiapine was associated with significant increase in quality of life compared to placebo (mean SMD 0.47). Quetiapine

Table 1 Study characteristics of included studies.

Pharmacological treatments							
Study	Study groups/number of participants	Mean doses (Range) (mg/days)	Trial duration (weeks)	Minimum age	Mean age	Diagnosis	Study design
Allard et al. (2004)	Venlafaxine: $n=76$ Citalopram: $n=75$	V: 116 (75-150) C: 26 (20-30)	8/22	64	73,1	DSM-IV major depression	DB-RCT
Anon (2003)	Nortriptyline: $n=34$ Venlafaxine: $n=34$	N: 62,5 (50-100) V: 251,47 (225-300)	26	65	70,83	DSM-IV unipolar major depression	SB-RCT
Bocksberger et al. (1993)	Fluvoxamine: $n=20$ Moclobemide: $n=20$	F: 172 (100-200) M: 433 (300-450)	4	65	74,45	DSM-III major depressive episode	DB-RCT
Brion et al. (1996)	Tianeptine: $n=209$ Mianserin: $n=106$	T: 31,25 (25-37,5) M: 30	26	70	78,53	DSM-III-R depression majeure	DB-RCT
Cassano et al. (2002)	Fluoxetine: $n=119$ Paroxetine: $n=123$	F: 20-66 P: 20-40	6/20	65	75,24	ICD-10 depression (paragraphs F32, F32.1 and F322	DB-RCT
Chen et al. (2011)	Escitalopram: $n=29$ Placebo $n=26$	E: 10	8	65	68,9	DSM-IV major depression	DB-RCT
Cohn et al. (1990)	Sertraline: $n=161$ Amitriptyline: $n=80$	S: 116 (50-200) A: 88 (50-150)	8	63	70,33	DSM-III major depression or bipolar disorder	DB-RCT
Dorman (1992)	Mianserin: $n=28$ Paroxetine: $n=29$	M: 60 P: 30	6	65	-	DSM-III unipolar depression	DB-RCT
EUCTR-001,829-33-FR 2008	Placebo: $n=121$ Duloxetine: $n=249$	D: 60	12/25	65	72,89	DSM-IV-TR Major Depressive Disorder	DB-RCT
EUCTR-003,821-25-DK 2005	Placebo: $n=$ - Escitalopram: $n=99$	E: 10	12	65	70,3	ICD-10 depressive single episode, depressive recurrent episode or organic depressive episode	DB-RCT
EUCTR-005,612-26-SK 2013	Escitalopram: $n=99$ Placebo: $n=107$ Tianeptine: $n=105$	E: 10 T: 25-50	8	65	70,44	DSM-IV-T Major Depressive Episode	DB-RCT
Finkel et al. (1999b)	Fluoxetine: $n=33$ Sertraline: $n=42$	F: 28,5 (20-40) S: 72,6 (50-100)	12	70	74,44	DSM-III-R major depression	DB-RCT

(*continued on next page*)

Table 1 (*continued*)

Pharmacological treatments

Study	Study groups/number of participants	Mean doses (Range) (mg/days)	Trial duration (weeks)	Minimum age	Mean age	Diagnosis	Study design
Finkel et al. (1999a)	Sertraline: $n = 39$ Nortriptyline: $n = 37$	S: 102 (50-150) N: - (25-100)	12	70	74,49	DSM-III-R major depression	DB-RCT
Geretsegger et al. (1995)	Paroxetine: $n = 44$ Amitriptyline: $n = 47$	P: 20-30 A: 100-150	6	65	71,15	DSM-III major depression	DB-RCT
GlaxoSmithKline (1991a)	Dothiepin: $n = 67$ Paroxetine: $n = 67$	D: 75 P: 20	6	65	75,85	DSM-III-R major depressive episode	DB-RcT
GlaxoSmithKline (1991b)	Paroxetine: $n = 6$ Clomipramine: $n = 5$	P: 20-40 C: 25-100	14	65	83,2	DSM-III major depressive episode	DB-RCT
GlaxoSmithKline (1993)	Paroxetine: $n = 57$ Lofepramine: $n = 49$	P: 20-30 L: 70-320	8	65	75,27	DSM-III-R major depressive episode	DB-RCT
Guelfi et al. (1999)	Tianeptine: $n = 115$ Fluoxetine: $n = 122$	T: 25-37,5 F: 20	12	65	77,56	DSM-III-R major depressive episode	DB-RCT
Heun et al. (2013)	Placebo: $n = 71$ Agomelatine: $n = 151$	A: 25 50	8	65	71,84	DSM-IV-TR moderate to severe episode of recurrent MDD	DB-RCT
Hewett et al. (2010)	Placebo: $n = 208$ Bupropion: $n = 212$	B: 179 (150-300)	10	65	71,10	DSM-IV MDD	DB-RCT
Hutchinson et al. (1992)	Amitriptyline: $n = 32$ Paroxetine: $n = 58$	A: 100 P: 30	6	65	71,82	DSM-III major depressive disorder	DB-RCT
Jansen et al. (2003)	Nortriptyline/ paroxetine	N: 25-72 P: 10-20	4	71	82	DSM-IV with major depressive or dysthymic disorders	DB-RCT
Karlsson et al. (2000)	Citalopram: $n = 163$ Mianserin: $n = 173$	C: 28 (20-40) M: 40 (30-60)	12	64	75,17	DSM-III-R major depression	DB-RCT
Kasper et al. (2005)	Fluoxetine: $n = 164$ Placebo: $n = 180$ Escitalopram: $n = 174$	F: 20 E: 10	8	65	75	DSM-IV MDD	DB-RCT

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Table 1 (*continued*)

Pharmacological treatments

Study	Study groups/number of participants	Mean doses (Range) (mg/days)	Trial duration (weeks)	Minimum age	Mean age	Diagnosis	Study design
Katila et al. (2013)	Placebo: $n=172$ Quetiapine: $n=166$	Q: 158,7 (50-300)	9	66	71,25	DSM-IV single or recurrent MDD	DB-RCT
Katona et al. (1999)	Imipramine: $n=109$ Reboxetine: $n=109$	I: 50-100 R: 4-6	8	65	74,15	DSM-III-R MDD	DB-RCT
Katona et al. (2012)	Duloxetine: $n=151$ Vortioxetine: $n=156$ Placebo: $n=145$	D: 60 V: 5	8	65	70,57	DSM-IV MDD	DB-RCT
Kyle et al. (1998)	Citalopram: $n=179$ Amitriptyline: $n=186$	C: 24 (20-40) A: 57 (50-100)	8	65	73,76	DSM-III-R major depression	DB-RCT
Mahapatra and Hackett (1997)	Dothiepin: $n=48$ Venlafaxine: $n=44$	D: 50-150 V: 50-150	6	64	74	DSM-III-R major depression	DB-RCT
Nair et al. (1993)	Doxepin: $n=19$ Trimipramine: $n=18$	D: 138 (100-200) T: 144 (100-200)	5	-	69,38	DSM-III Major Depressive Episode	DB-RCT
NCT00130455 2006	Escitalopram/ Placebo						
Newhouse et al. (1995)	Fluoxetine: $n=33$ Sertraline: $n=42$	F: 20-40 S: 50-100	12	70	74,4	DSM-III-R major depressive disorder	DB-RCT
Phanjoo et al. (1991)	Mianserin: $n=25$ Fluvoxamine: $n=25$	M: 60 (40-80) F: 170 (100-200)	6	66	76,5	DSM-III major depressive episode	DB-RCT
Rahman et al. (1991)	Fluvoxamine: $n=26$ Dothiepin: $n=26$	F: 157 (100-200) D: 159 (100-200)	6	61	74	DSM-III major depressive episode	DB-RCT
Raskin et al. (2007)	Placebo: $n=104$ Duloxetine: $n=207$	D: 60	8	65	72,86	DSM-IV recurrent major depressive disorder	DB-RCT
Robinson et al. (2014)	Duloxetine: $n=249$ Placebo: $n=121$	D: 60	12	65	73,04	DSM-IV-TR Major Depressive Disorder	DB-RCT
Roose et al. (2004)	Citalopram: $n=84$ Placebo: $n=91$	C: 10-40	8	75	79,59	DSM-IV unipolar depression, single or recurrent, nonpsychotic	DB-RCT

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Table 1 (*continued*)

Pharmacological treatments

Study	Study groups/number of participants	Mean doses (Range) (mg/days)	Trial duration (weeks)	Minimum age	Mean age	Diagnosis	Study design
Schatzberg et al. (2002)	Mirtazapine: $n = 128$ Paroxetine: $n = 126$	M: 34 (15-45) P: 34 (20-40)	8	65	71,85	DSM-IV single or recurrent major depressive episode	DB-RCT
Schatzberg and Roose (2006)	Venlafaxine: $n = 104$ Placebo: $n = 96$ Fluoxetine: $n = 100$	V: 225 (75-225) F: - (20-60)	8	65	71	DSM-IV unipolar depression (single or recurrent, nonpsychotic)	DB-RCT
Schifano et al. (1990)	Mianserin: $n = 25$ Maprotiline: $n = 23$	Mi: 67,6-90 Ma: 112,5-150	4	65	75,41	DSM-III a major depressive episode	DB-RCT
Schone and Ludwig (1993)	Fluoxetine: $n = 52$ Paroxetine: $n = 54$	F: 20-60 P: 20-40	6	61	74,01	DSM-III-R current episode of major depression	DB-RCT
Schweizer et al. (1998)	Imipramine: $n = 60$ Buspirone: $n = 57$ Placebo: $n = 60$	I: 89 (25-150) B: 38 (10-60)	8	65	72	DSM-III-R unipolar major depression	DB-RCT
Smeraldi et al. (1997)	Venlafaxine: $n = 55$ Clomipramine: $n = 58$ Trazodone: $n = 57$	V: 75-150 C: 50-100 T: 150-300	6	65	71	DSM-III-R major depression	DB-RCT
Study 032a	Reboxetine: $n = 24$ Placebo: $n = 26$	R: 4-6	8	63	79,96	DSM-III-R Major Depressive Disorder not accompanied by psychotic features	DB-RCT
Tignol et al. (1998)	Imipramine: $n = 107$ Milnacipran: $n = 112$	I: 75-100 M: 75-100	8	65	74,10	DSM-III-R MDE with or without melancholia and without psychotic features	DB-RCT

Non-pharmacological treatments

Study	Study groups/number of participants	Trial duration (weeks)	Minimum Age	Mean Age	Diagnosis	Study design
Ahmadpanah et al. (2017)	Control (leisure activities): $n = 17$ Detached mindfulness condition: $n = 19$	4	65	69,18	DSM-V Major Depressive Episode	SB-RCT

Table 1 Study characteristics of included studies.

Non-pharmacological treatments						
Study	Study groups/number of participants	Trial duration (weeks)	Minimum Age	Mean Age	Diagnosis	Study design
*ACTRN12616001412426 (2016)	Treatment as Usual/behavioural activation	12	65	-	DSM-V Major Depressive Episode	SB-RCT
*Azar et al. (2010)	enhanced specialty referral model/integrated care model	-	65	-	DSM-IV major depression	DB-RCT
Bosanquet et al. (2017)	Treatment as Usual: $n = 236$ Collaborative care: $n = 249$	16	64	72,16	DSM-IV Major Depressive Disorder	OL-RCT
Ekkers et al. (2011)	Competitive Memory Training: $n = 53$ Treatment as Usual: $n = 40$	7	65	72,70	DSM-IV-TR major depressive disorder	SB-RCT
Klug et al. (2010)	Treatment as Usual: $n = 30$ Geriatric home treatment group: $n = 30$	12/52	64	74,9	ICD-10 major depression	OL-RCT
Serfaty et al. (2009)	Talking Control: $n = 67$ Treatment as Usual: $n = 67$ Cognitive Behavioral Therapy: $n = 70$	16/43	65	74,07	DSM-IV major depression	SB-RCT
*NCT01908673 (August)	Automatic Self Transcending Meditation/ HRV biofeedback					

* No usable data reported.

was also associated with significantly better quality of life compared to citalopram, duloxetine and bupropion (mean SMDs 0.54, 0.33, 0.31) (eTab5). Only bupropion showed significant improvement in social functioning compared to placebo (SMD 0.26) (eTab6).

3.9. Anticholinergic side-effects

Quetiapine, dothiepin, duloxetine, reboxetine, mirtazapine, amitriptyline and imipramine associated with more anticholinergic side-effects compared to placebo (mean RRs 1.96, 2.63, 3.02, 3.36, 3.56, 3.65, 3.87) Fig. 4a and compared with tianeptine, citalopram and fluoxetine. Escitalopram and vortioxetine were better compared to all interventions mentioned at the beginning of this section, with the exception of dothiepine. Duloxetine, reboxetine, mirtazapine, amitriptyline and imipramine were associated with significantly more anticholinergic side-effects compared to several other drugs (eTab7). Furthermore fluoxetine was associated with less side-effects compared to venlafaxine and quetiapine (RRs 0.52 and 0.43), sertraline with less than nortriptyline (RR 0.55) and milnacipran with less than imipramine (RR 0.48). For separate results of specific anticholinergic events, see eAppendix6-7.

3.10. Anxiety symptoms

There were no significant differences between any intervention and placebo. Venlafaxine was associated with significantly less anxiety compared to fluoxetine and paroxetine (mean RRs 0.20 and 0.11) (eTab8).

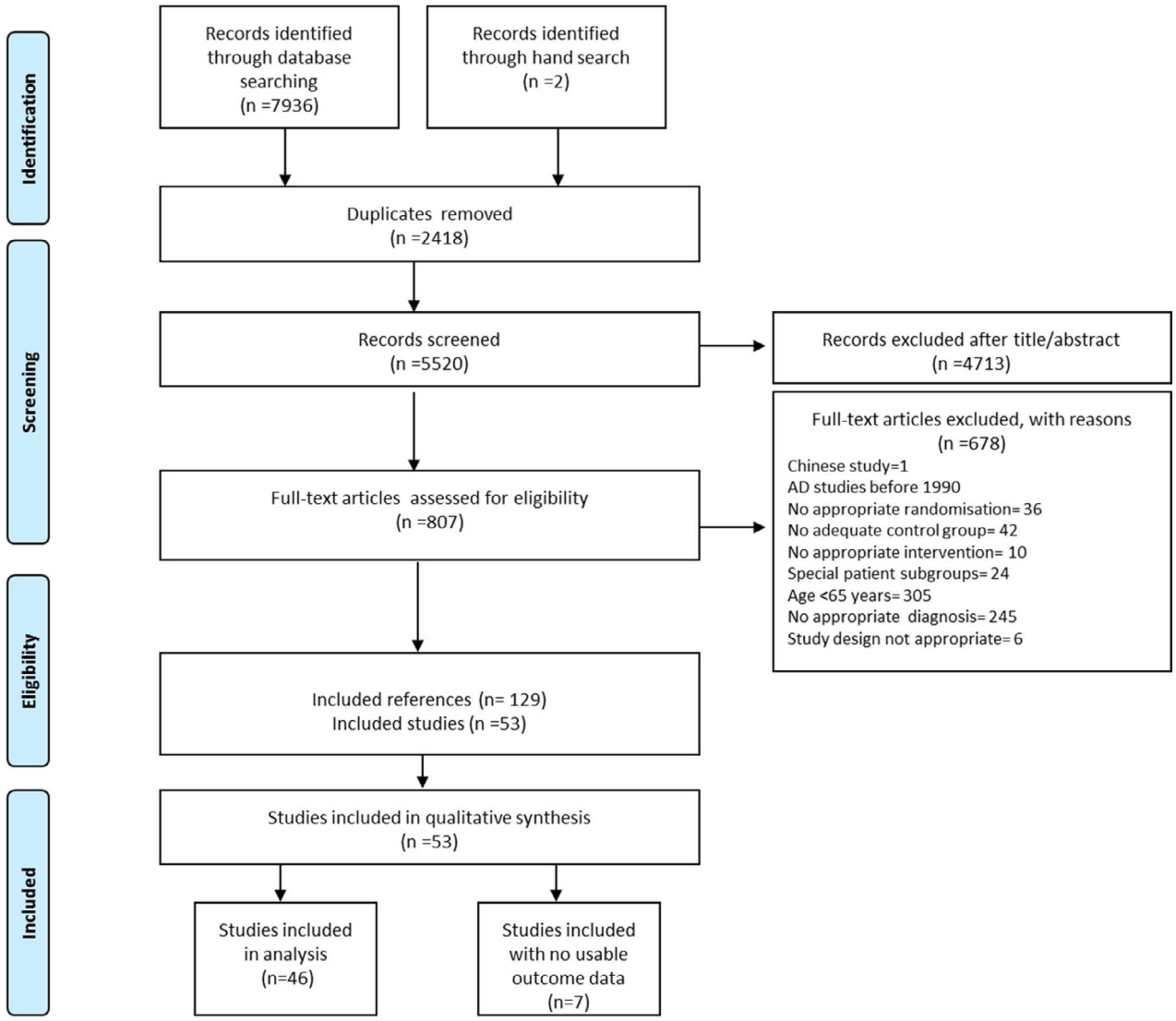

Fig. 1 Prisma flow-chart for study selection.

3.11. Diarrhoea

Milnacipran and imipramine were associated with significantly fewer patients with diarrhoea than placebo (mean RRs 0.02, 0.05) Fig. 4j, and duloxetine was associated with more patients with diarrhoea compared to placebo (RR 2.31). Milnacipran was associated with less diarrhoea compared to most of the other antidepressants and quetiapine. Lofepramine, imipramine, tianeptine, mirtazapine and paroxetine were associated with significantly fewer patients with diarrhoea compared to citalopram, duloxetine and agomelatine. Finally imipramine was associated with less diarrhoea compared to fluoxetine (RR 0.05) (eTab10).

3.12. Dizziness

Duloxetine, venlafaxine and imipramine were associated with significantly more dizziness compared to placebo (mean RRs 1.81, 2.69 and 2.86) Fig. 4f, and tianeptine was associated with fewer events compared to placebo (RR 0.27). Tianeptine was associated with significantly less dizziness compared to quetiapine and most of the other antidepressants. Imipramine and venlafaxine were associated with significantly more dizziness compared to some other antidepressants (eTab11).

3.13. Dyspeptic signs and symptoms

Imipramine was associated with significantly fewer patients with dyspeptic signs compared to placebo Fig 4i, fluoxetine and citalopram (RRs 0.39, 0.24, 0.12) (eTab13).

3.14. Hyperhidrosis

Imipramine, duloxetine, reboxetine and venlafaxine were associated with significantly more hyperhidrosis compared to placebo (mean RRs 4.00, 3.84, 5.71, 10.15)

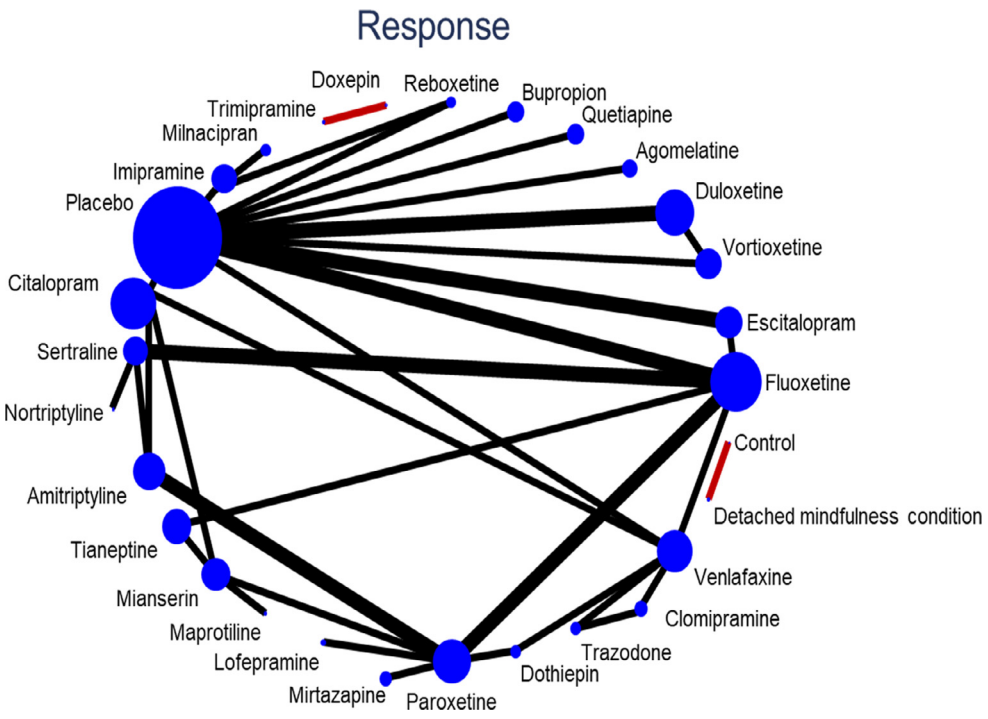

Fig. 2 Network plot for the primary outcome.
The size of the nodes corresponds to the number of trials that study the treatments. The (directly) comparable treatments are linked with a line. The thickness of the line corresponds to the inverse variance of the number of direct comparisons.

Quetiapine	Quetiapine	1.26 (0.63,2.51)	1.42 (0.61,3.31)	1.52 (0.78,2.97)	**1.57 (1.07,2.32)**	1.70 (0.94,3.07)	**1.76 (1.11,2.80)**	1.84 (0.90,3.74)	**2.00 (1.21,3.30)**	**2.01 (1.31,3.11)**	2.11 (0.44,10.05)	**2.03 (1.28,3.23)**	**2.09 (1.40,3.12)**	2.20 (0.48,10.17)	2.33 (0.47,11.59)	**2.38 (1.76,3.23)**	**2.50 (1.69,3.69)**	**2.84 (1.13,7.15)**	**2.91 (1.85,4.56)**	**3.27 (2.22,4.83)**	**5.68 (3.35,9.62)**			
1.14 (0.64,2.02)	Duloxetine	Mirtazapine	1.13 (0.41,3.09)	1.21 (0.75,1.95)	1.25 (0.64,2.44)	1.35 (0.94,1.93)	1.40 (0.69,2.86)	1.46 (0.86,2.49)	1.59 (0.87,2.90)	1.60 (0.90,2.87)	1.68 (0.32,8.76)	1.62 (0.92,2.84)	1.66 (0.85,3.27)	1.75 (0.34,8.89)	1.86 (0.34,10.09)	**1.90 (1.02,3.53)**	**1.99 (1.03,3.82)**	2.26 (0.85,6.03)	**2.31 (1.24,4.33)**	**2.61 (1.40,4.85)**	**4.52 (2.21,9.24)**			
1.36 (0.64,2.92)	1.20 (0.59,2.43)	Mirtazapine	Agomelatine	1.07 (0.40,2.88)	1.11 (0.49,2.53)	1.20 (0.47,3.06)	1.24 (0.52,2.94)	1.30 (0.47,3.58)	1.41 (0.58,3.41)	1.42 (0.61,3.31)	1.49 (0.27,8.32)	1.43 (0.61,3.39)	1.47 (0.64,3.38)	1.55 (0.28,8.45)	1.64 (0.28,9.56)	1.68 (0.76,3.70)	1.76 (0.77,4.02)	2.00 (0.62,6.49)	2.05 (0.87,4.82)	**2.31 (1.01,5.27)**	**4.00 (1.63,9.83)**			
1.35 (0.69,2.66)	1.18 (0.64,2.20)	0.99 (0.44,2.21)	Imipramine	Dothiepin	1.04 (0.54,1.98)	1.12 (0.82,1.53)	1.16 (0.58,2.32)	1.21 (0.73,2.00)	1.32 (0.74,2.34)	1.33 (0.76,2.31)	1.39 (0.27,7.19)	1.34 (0.78,2.29)	1.38 (0.72,2.65)	1.45 (0.29,7.29)	1.54 (0.28,8.28)	1.57 (0.86,2.85)	1.64 (0.88,3.09)	1.87 (0.71,4.92)	**1.92 (1.05,3.50)**	**2.16 (1.19,3.92)**	**3.74 (1.87,7.49)**			
1.36 (0.73,2.53)	1.19 (0.80,1.79)	1.00 (0.47,2.11)	1.01 (0.52,1.96)	Vortioxetine	Duloxetine	1.08 (0.61,1.89)	1.12 (0.82,1.54)	1.17 (0.59,2.32)	1.27 (0.79,2.03)	1.28 (0.86,1.90)	1.34 (0.28,6.32)	1.29 (0.85,1.98)	1.33 (0.93,1.90)	1.40 (0.31,6.40)	1.48 (0.30,7.30)	**1.52 (1.19,1.93)**	**1.59 (1.12,2.24)**	1.81 (0.73,4.46)	**1.85 (1.22,2.79)**	**2.08 (1.48,2.94)**	**3.61 (2.20,5.92)**			
1.37 (0.70,2.66)	1.20 (0.65,2.20)	1.00 (0.46,2.20)	1.01 (0.50,2.05)	1.00 (0.52,1.92)	Agomelatine	Paroxetine	1.04 (0.56,1.93)	1.08 (0.73,1.60)	1.18 (0.73,1.91)	1.19 (0.75,1.88)	1.24 (0.25,6.24)	1.20 (0.78,1.85)	1.23 (0.70,2.18)	1.30 (0.27,6.32)	1.37 (0.26,7.19)	1.40 (0.85,2.33)	1.47 (0.85,2.54)	1.68 (0.67,4.17)	**1.71 (1.03,2.86)**	**1.93 (1.16,3.20)**	**3.35 (1.80,6.21)**			
1.35 (0.61,3.01)	1.18 (0.56,2.52)	0.99 (0.40,2.46)	1.00 (0.65,1.54)	0.99 (0.45,2.18)	0.99 (0.43,2.26)	Milnacipran	Vortioxetine	1.04 (0.50,2.17)	1.13 (0.67,1.93)	1.14 (0.72,1.83)	1.20 (0.25,5.76)	1.15 (0.70,1.89)	1.19 (0.77,1.84)	1.25 (0.27,5.84)	1.32 (0.26,6.65)	1.35 (0.95,1.92)	1.42 (0.92,2.18)	1.61 (0.63,4.13)	**1.65 (1.02,2.68)**	**1.86 (1.21,2.85)**	**3.22 (1.85,5.62)**			
1.42 (0.66,3.06)	1.25 (0.61,2.55)	1.04 (0.43,2.53)	1.05 (0.69,1.61)	1.04 (0.49,2.22)	1.04 (0.47,2.30)	1.05 (0.57,1.93)	Reboxetine	Lofepramine	1.09 (0.58,2.02)	1.10 (0.60,2.00)	1.15 (0.22,6.03)	1.11 (0.62,1.99)	1.14 (0.57,2.27)	1.20 (0.23,6.12)	1.27 (0.23,6.94)	1.30 (0.68,2.46)	1.36 (0.69,2.66)	1.55 (0.57,4.17)	1.58 (0.83,3.02)	1.78 (0.94,3.38)	**3.09 (1.48,6.42)**			
1.61 (0.87,3.00)	1.41 (0.81,2.46)	1.18 (0.76,1.83)	1.19 (0.61,2.34)	1.18 (0.65,2.16)	1.18 (0.61,2.27)	1.19 (0.54,2.65)	1.13 (0.52,2.45)	Paroxetine	Sertraline	1.01 (0.76,1.34)	1.06 (0.22,5.14)	1.02 (0.82,1.27)	1.05 (0.65,1.69)	1.10 (0.23,5.21)	1.17 (0.23,5.93)	1.19 (0.80,1.78)	1.25 (0.79,1.97)	1.42 (0.66,3.08)	1.46 (0.99,2.14)	**1.64 (1.08,2.49)**	**2.84 (1.64,4.92)**			
1.60 (0.71,3.59)	1.40 (0.66,2.99)	1.17 (0.59,2.31)	1.18 (0.51,2.76)	1.17 (0.53,2.60)	1.17 (0.51,2.69)	1.18 (0.46,3.06)	1.12 (0.44,2.85)	0.99 (0.59,1.66)	Lofepramine	Citalopram	1.05 (0.22,4.99)	1.01 (0.84,1.22)	1.04 (0.69,1.56)	1.09 (0.24,5.06)	1.16 (0.23,5.76)	1.18 (0.87,1.61)	1.24 (0.85,1.81)	1.41 (0.62,3.22)	**1.44 (1.10,1.90)**	**1.63 (1.15,2.29)**	**2.82 (1.72,4.62)**			
1.67 (0.85,3.26)	1.46 (0.79,2.69)	1.22 (0.67,2.23)	1.23 (0.60,2.52)	1.22 (0.63,2.35)	1.22 (0.61,2.46)	1.23 (0.54,2.84)	1.17 (0.52,2.62)	1.03 (0.68,1.56)	1.04 (0.54,2.02)	Dothiepin	Imipramine	0.96 (0.20,4.63)	0.99 (0.21,4.68)	1.04 (0.77,1.41)	1.10 (0.76,1.60)	1.13 (0.24,5.22)	1.18 (0.25,5.57)	1.35 (0.23,7.84)	1.38 (0.29,6.60)	1.55 (0.33,7.31)	2.69 (0.55,13.19)			
1.70 (0.92,3.16)	1.49 (0.86,2.60)	1.25 (0.59,2.63)	1.26 (0.65,2.44)	1.25 (0.68,2.28)	1.25 (0.65,2.39)	1.26 (0.57,2.77)	1.20 (0.56,2.54)	1.06 (0.58,1.93)	1.06 (0.48,2.36)	1.02 (0.53,1.97)	Bupropion	Amitriptyline	1.03 (0.67,1.59)	1.08 (0.23,5.05)	1.15 (0.23,5.75)	1.17 (0.83,1.66)	1.23 (0.82,1.85)	1.40 (0.63,3.12)	**1.43 (1.03,1.98)**	**1.61 (1.11,2.34)**	**2.79 (1.67,4.67)**			
1.79 (0.98,3.27)	1.57 (0.92,2.68)	1.31 (0.77,2.23)	1.32 (0.69,2.55)	1.31 (0.73,2.36)	1.31 (0.69,2.48)	1.32 (0.61,2.89)	1.26 (0.59,2.67)	1.11 (0.82,1.50)	1.12 (0.62,2.03)	1.07 (0.68,1.70)	1.05 (0.59,1.89)	Amitriptyline	Bupropion	1.05 (0.23,4.83)	1.12 (0.23,5.50)	1.14 (0.88,1.48)	1.19 (0.83,1.71)	1.36 (0.55,3.37)	1.39 (0.91,2.12)	**1.57 (1.10,2.24)**	**2.71 (1.64,4.49)**			
1.79 (0.97,3.31)	1.57 (0.91,2.72)	1.31 (0.72,2.40)	1.33 (0.69,2.57)	1.32 (0.72,2.39)	1.31 (0.69,2.51)	1.33 (0.60,2.92)	1.26 (0.59,2.68)	1.11 (0.74,1.68)	1.12 (0.58,2.17)	1.08 (0.64,1.81)	1.05 (0.58,1.91)	1.00 (0.70,1.43)	Sertraline	Reboxetine	1.06 (0.66,1.71)	1.08 (0.24,4.86)	1.13 (0.25,5.19)	1.29 (0.23,7.33)	1.32 (0.28,6.15)	1.49 (0.33,6.81)	2.58 (0.54,12.30)			
2.00 (1.09,3.67)	**1.76 (1.02,3.01)**	1.47 (0.74,2.89)	1.48 (0.77,2.85)	1.47 (0.81,2.65)	1.47 (0.77,2.78)	1.48 (0.68,3.24)	1.41 (0.66,2.99)	1.24 (0.74,2.08)	1.25 (0.60,2.60)	1.20 (0.67,2.17)	1.18 (0.65,2.12)	1.12 (0.67,1.86)	1.12 (0.67,1.87)	Escitalopram	Milnacipran	1.02 (0.21,4.94)	1.07 (0.22,5.27)	1.22 (0.20,7.37)	1.25 (0.25,6.24)	1.40 (0.29,6.91)	2.43 (0.48,12.46)			
2.03 (1.14,3.63)	**1.78 (1.07,2.96)**	1.49 (0.82,2.71)	1.50 (0.80,2.82)	1.49 (0.85,2.62)	1.49 (0.81,2.75)	1.50 (0.70,3.22)	1.43 (0.69,2.96)	1.26 (0.84,1.89)	1.27 (0.66,2.45)	1.22 (0.81,1.84)	1.19 (0.68,2.09)	1.14 (0.77,1.68)	1.13 (0.73,1.75)	1.02 (0.62,1.67)	Venlafaxine	Placebo	1.05 (0.82,1.34)	1.19 (0.50,2.85)	1.22 (0.88,1.70)	1.37 (1.08,1.75)	2.38 (1.55,3.66)			
2.07 (1.17,3.64)	**1.81 (1.11,2.97)**	1.51 (0.85,2.70)	1.53 (0.83,2.83)	1.52 (0.88,2.62)	1.51 (0.83,2.76)	1.53 (0.72,3.24)	1.45 (0.71,2.97)	1.28 (0.88,1.87)	1.29 (0.68,2.45)	1.24 (0.78,1.97)	1.21 (0.70,2.10)	1.15 (0.84,1.59)	1.15 (0.77,1.72)	1.03 (0.64,1.68)	1.02 (0.73,1.41)	Citalopram	Escitalopram	1.14 (0.46,2.79)	1.16 (0.78,1.73)	1.31 (0.99,1.74)	2.27 (1.45,3.58)			
2.09 (1.33,3.28)	**1.83 (1.29,2.62)**	1.53 (0.83,2.83)	1.55 (0.93,2.57)	1.54 (1.00,2.35)	1.53 (0.94,2.51)	1.55 (0.80,3.01)	1.47 (0.79,2.74)	1.30 (0.85,1.99)	1.31 (0.67,2.56)	1.26 (0.76,2.07)	1.23 (0.80,1.88)	1.17 (0.78,1.75)	1.17 (0.77,1.77)	1.04 (0.70,1.57)	1.03 (0.71,1.48)	1.01 (0.72,1.43)	Placebo	Nortriptyline	1.02 (0.43,2.43)	1.15 (0.48,2.78)	2.00 (0.77,5.16)			
2.20 (1.06,4.54)	**1.93 (0.99,3.77)**	1.61 (0.77,3.37)	1.63 (0.76,3.49)	1.61 (0.79,3.29)	1.61 (0.76,3.42)	1.63 (0.68,3.91)	1.55 (0.66,3.61)	1.36 (0.75,2.47)	1.37 (0.63,3.02)	1.32 (0.72,2.40)	1.29 (0.63,2.63)	1.23 (0.68,2.21)	1.23 (0.66,2.27)	1.10 (0.57,2.13)	1.08 (0.70,1.67)	1.06 (0.62,1.83)	1.05 (0.59,1.86)	Clomipramine	Venlafaxine	1.13 (0.79,1.61)	1.95 (1.18,3.23)			
2.43 (1.30,4.54)	**2.13 (1.22,3.73)**	1.78 (0.94,3.37)	1.80 (0.93,3.50)	1.79 (0.97,3.28)	1.78 (0.93,3.43)	1.80 (0.82,3.97)	1.71 (0.81,3.63)	1.51 (0.95,2.39)	1.52 (0.76,3.04)	1.46 (0.85,2.51)	1.43 (0.78,2.62)	1.36 (0.88,2.09)	1.36 (0.85,2.17)	1.22 (0.70,2.10)	1.20 (0.77,1.86)	1.18 (0.83,1.66)	1.16 (0.76,1.79)	1.11 (0.60,2.06)	Mianserin	Fluoxetine	**1.73 (1.21,2.47)**			
2.62 (1.25,5.48)	**2.30 (1.16,4.55)**	1.92 (0.90,4.07)	1.94 (0.89,4.21)	1.92 (0.93,3.97)	1.92 (0.89,4.12)	1.94 (0.80,4.71)	1.84 (0.78,4.35)	1.62 (0.88,2.99)	1.64 (0.74,3.64)	1.57 (0.85,2.91)	1.54 (0.75,3.17)	1.46 (0.80,2.67)	1.46 (0.78,2.75)	1.31 (0.66,2.57)	1.29 (0.81,2.04)	1.27 (0.72,2.22)	1.25 (0.70,2.25)	1.19 (0.75,1.90)	1.08 (0.57,2.03)	Trazodone	Tianeptine			
2.48 (1.44,4.25)	**2.17 (1.37,3.46)**	**1.82 (1.03,3.21)**	**1.83 (1.02,3.31)**	**1.82 (1.08,3.06)**	**1.81 (1.02,3.23)**	1.83 (0.88,3.80)	1.74 (0.87,3.48)	**1.54 (1.07,2.21)**	1.55 (0.82,2.92)	1.49 (0.93,2.37)	1.46 (0.87,2.45)	1.38 (0.98,1.96)	**1.38 (1.00,1.91)**	1.24 (0.82,1.88)	1.22 (0.86,1.73)	1.20 (0.86,1.66)	1.18 (0.88,1.60)	1.13 (0.64,1.97)	1.02 (0.69,1.50)	0.95 (0.53,1.69)	Fluoxetine			
2.63 (1.41,4.91)	**2.30 (1.31,4.04)**	**1.93 (1.01,3.67)**	**1.94 (1.00,3.79)**	**1.93 (1.05,3.55)**	**1.92 (1.00,3.71)**	1.94 (0.88,4.30)	1.85 (0.87,3.94)	**1.63 (1.02,2.61)**	1.64 (0.82,3.31)	1.58 (0.91,2.74)	1.54 (0.84,2.83)	1.47 (0.93,2.31)	1.46 (0.92,2.32)	1.31 (0.77,2.24)	1.29 (0.82,2.04)	1.27 (0.85,1.91)	1.26 (0.81,1.94)	1.20 (0.64,2.25)	1.08 (0.76,1.54)	1.00 (0.53,1.92)	1.06 (0.74,1.51)	Tianeptine		
3.59 (1.36,9.47)	**3.15 (1.24,7.98)**	**2.63 (1.00,6.90)**	2.66 (0.98,7.22)	**2.64 (1.01,6.88)**	2.63 (0.98,7.09)	2.66 (0.90,7.89)	2.53 (0.87,7.32)	2.23 (0.95,5.25)	2.25 (0.83,6.11)	2.16 (0.87,5.38)	2.11 (0.81,5.50)	2.01 (0.87,4.61)	2.00 (0.95,4.24)	1.79 (0.72,4.45)	1.77 (0.74,4.21)	1.74 (0.74,4.07)	1.72 (0.73,4.05)	1.63 (0.62,4.32)	1.48 (0.61,3.58)	1.37 (0.51,3.66)	1.45 (0.64,3.28)	1.37 (0.57,3.30)	Nortriptyline	
3.84 (1.36,10.82)	**3.37 (1.24,9.14)**	2.81 (0.99,7.99)	2.84 (0.98,8.21)	**2.82 (1.01,7.86)**	2.81 (0.98,8.08)	2.84 (0.90,8.92)	2.70 (0.88,8.26)	2.38 (0.92,6.14)	2.40 (0.82,7.06)	2.30 (0.86,6.19)	2.25 (0.81,6.29)	2.14 (0.84,5.46)	2.14 (0.83,5.54)	1.92 (0.71,5.17)	1.89 (0.74,4.82)	1.86 (0.76,4.55)	1.83 (0.72,4.67)	1.75 (0.62,4.91)	1.58 (0.69,3.61)	1.47 (0.52,4.16)	1.55 (0.62,3.86)	1.46 (0.59,3.60)	1.07 (0.32,3.59)	Maprotiline

Fig. 3 Results of network meta-analysis – Response (red), Remission (blue).
The table shows the treatment effects for the primary outcome response (lower left portion) and the remission (upper right portion). Drugs are reported in order of their individual SUCRA- ranking, which should be interpreted carefully, because the precision of effects is low for most of the comparisons. Effects are expressed as risk ratios (RRs). Bold and underlined values are significant. Comparisons between treatments should be read from left to right, with the relevant estimate being in the common cell for the column-defining treatment and the row-defining treatment. For response, RRs $>$ 1 indicate that the treatment specified in the column is more efficacious than that in the row. For remission, RRs $>$ 1 indicate that the treatment specified in the row leads to more patients in remission than that in the column.

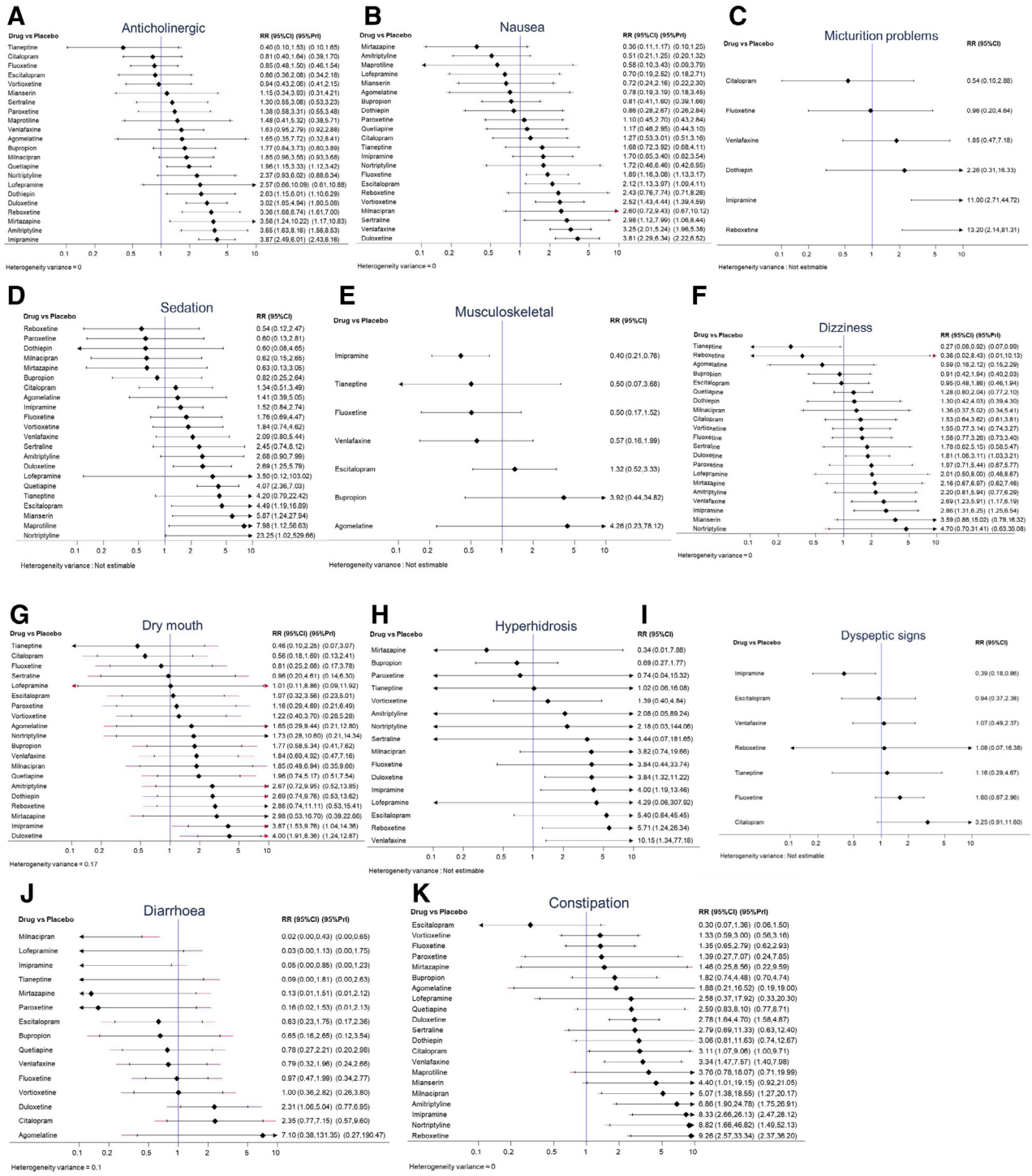

Fig. 4 Forest-plots of network meta-analyses for side-effects.

Fig. 4h and in comparison with bupropion (RR 5.82, 5.59, 8.32, 14.78). Mirtazapine was associated with less hyperhidrosis compared to fluoxetine and venlafaxine (RR 0.09 and 0.03). Paroxetine was associated with fewer hyperhidrosis compared to venlafaxine (RR 0.07), and vortioxetine with less compared to duloxetine (RR 0.36) (eTab14).

3.15. Insomnia

Maprotiline and mianserin were associated with significantly less insomnia compared to citalopram, imipramine, bupropion, escitalopram, venlafaxine and fluoxetine (mean RRs 0.32, 0.14, 0.13, 0.12, 0.12, 0.12 and 0,37, 0.16, 0.15, 0.14, 0.14, 0.13) (eTab15).

3.16. Micturition problems

Imipramine and reboxetine were associated with significantly more micturition problems compared to placebo Fig 4c (mean RRs 11.00, 13.20). Citalopram and fluoxetine caused significantly fewer problems compared to imipramine (RRs 0.05 and 0.09) and compared to reboxetine (RRs 0.04 and 0.07) (eTab 16).

3.17. Musculoskeletal and connective tissue pain and discomfort

Imipramine was associated with significantly fewer musculoskeletal side-effects compared to placebo Fig 4e, escitalopram and bupropion (mean RRs 0.40, 0.30, 0.10) (eTab17).

3.18. Nausea

Fluoxetine, escitalopram, vortioxetine, sertraline, venlafaxine and duloxetine were associated with more nausea compared to placebo (mean RRs 1.89, 2.12, 2.52, 2.98, 3.25, 3.81) Fig. 4b. Mirtazapine and amitriptyline were associated with less nausea compared to several other antidepressants. Vortioxetine, sertraline, venlafaxine and duloxetine were associated with significantly more nausea compared to some other antidepressants (eTab18).

3.19. Sedation

Duloxetine, escitalopram, quetiapine, mianserin, maprotiline and nortriptyline were associated with more sedation compared to placebo (mean RRs 2.69, 4.49, 4.07, 5.87, 7.98, 23.25) Fig. 4d. Reboxetine, paroxetine, milnacipran and mirtazapine were associated with significantly less sedation compared to some other drugs. Escitalopram, quetiapine, mianserin, maprotiline and nortriptyline were associated with significantly higher sedation compared to several drugs. Finally citalopram was associated with less sedation compared to amitriptyline (RR 0.50) (eTab19).

3.20. Tremor

There were no significant differences between any intervention and placebo. Mirtazapine was associated with significantly less tremor compared to paroxetine (mean RR 0.35) (eTab20).

3.21. Weight gain

There was no placebo-controlled trial reporting data about the mean change of weight gain. Amitriptyline showed significantly more weight gain compared to fluoxetine, nortriptyline and sertraline (mean SMDs −1.17, −0.71, −0.71) (eTab21).

3.22. Other side-effects

Overall we conducted pairwise meta-analyses for 116 adverse events. Due to limited word count we are not able to present them all in the main text. Therefore, results are presented in eAppendix13. Only few significant differences were found.

3.23. Long-term results

As there were only six generally poorly reported studies with study duration longer than 12 weeks we only conducted pairwise meta-analyses. The only statistically significant results were that duloxetine was superior to placebo concerning depressive symptoms (mean SMD −0.39) and dropouts due inefficacy, but it produced more dropouts due to adverse events and anticholinergic side-effects than placebo (EUCTR2008-001829-33-FR, 2008). Venlafaxine produced more anticholinergic side effects than nortriptyline (RR 3.29), while nortriptyline was associated with more dizziness than venlafaxine (RR 2.25) (Anon, 2003). Finally, clomipramine produced more sedation than paroxetine (RR 2.57) (GlaxoSmithKline, 1991b) (see eAppendix14, eAppendix15).

3.24. Nonpharmacological interventions

Only five (Ahmadpanah et al., 2017; Bosanquet et al., 2017; Ekkers et al., 2011; Klug et al., 2010; Serfaty et al., 2009) out of eight included studies about non-pharmacological interventions provided usable data, and for each comparison only one trial was available. Therefore, neither network nor pairwise meta-analyses were possible. For this reason, we summarize here the results of single studies (also see eAppendix7).

In the 4-week study by Ahmadpanah et al. (2017), detached mindfulness condition (DMC, $n = 19$) showed a significantly higher remission rate (mean RR 18.90) and a significantly higher reduction of depressive symptoms (mean SMD −1.69) compared to the control group (leisure activities, $n = 17$). There were no significant effects in terms of response, and dropouts total. The sample size of the single trial was very small ($n = 36$).

In a study of 7 weeks duration ($n = 93$) by Ekkers et al. (2011), competitive memory training (CMTn = 53) was associated with significantly higher reduction of depressive symptoms compared to treatment as usual (TAU, $n = 40$) (SMD −0.53). TAU was associated with significantly more dropouts compared to CMT (RR 6.63).

In the study by (Klug et al., 2010) ($n = 60$), geriatric home treatment group (GHTG, $n = 30$) was associated with significantly higher reduction of depressive symptoms compared to treatment as usual (TAU, $n = 30$) (SMDs −1.05) in the short term (12 weeks). Furthermore GHTG improved quality of life and social functioning significantly more than TAU (SMDs −1.13 and −0.93). In the long term (52 weeks) GHTG was again associated with significantly higher reduction of depressive symptoms compared to treatment as usual (SMD -0.75). Furthermore GHTG improved social functioning and quality of life significantly more than TAU (SMDs 0.75, 0.75).

There were no statistically significant effects in terms of dropouts total.

In the study by Bosanquet et al. (2017) ($n = 485$) no short-term data was reported. In the long-term Collaborative Care (CC, $n = 249$) was associated with a significantly higher reduction of depressive symptoms (SMD −0.35), and fewer total dropouts (RR 0.10) compared to treatment as usual (TAU, $n = 236$).

In the study of 43 weeks by Serfaty et al. (2009) ($n = 204$) there were no statistically significant differences between Cognitive Behavioral Therapy (CBT, $n = 70$), Talking Control (TC, $n = 67$) and Treatment as Usual (TAU, $n = 67$) in terms of depressive symptoms, dropouts total, quality of life, and social functioning.

No side-effects were reported in any of the non-pharmacological interventions.

3.25. Consistency of the network and confidence in the estimates (CINeMA)

Although the check for transitivity did not reveal clear differences between treatments in key study characteristics (eAppendix8) the results showed significant overall inconsistency for the outcomes response (chi²: 32.96, p: 0.0003) and depressive symptoms (chi²: 61.02, p: 0.0000, also see discussion). For other efficacy outcomes no significant overall inconsistency was identified. There was also no significant overall inconsistency for side-effects, except for headaches (chi²: 12.62, p: 0.0272). It should be noted, however, that only very few studies were available per drug/comparison. Therefore transitivity could not be well explored, (eAppendix8), the statistical power of heterogeneity and inconsistency tests was limited, and for some comparisons it was not possible to estimate loop specific inconsistency due to missing direct evidence. For further details see eAppendix9. The assessments of confidence in the estimates using CINeMA was mainly moderate to very low, primarily due to study limitations (high risk of bias) and imprecision (eAppendix16), and due to the above described inconsistency of the primary outcome.

3.26. Meta-regression and sensitivity analyses for the primary outcome

Subgroup and meta-regression analyses showed no significant impact on the response rates for the moderators mean age, study duration, sponsorship or publication year. Neither had the sensitivity analyses excluding studies with high risk in the various risk of bias domains. When a fixed effects model was used more drugs were significantly superior to placebo, but this model is not appropriate in the presence of inconsistency. Other planned analyses were not feasible, due to insufficient data. (eAppendix10)

3.27. Small-study effects and publication bias

Funnel-plots were not meaningful, because most comparisons included only 1 or 2 studies and maximally three studies.

4. Discussion

To our knowledge, this is the first network-meta-analysis which evaluates all pharmacological and non-pharmacological interventions in older patients with MDD, and we analysed a broad spectrum of efficacy and tolerability outcomes. In terms of the primary outcome response to treatment quetiapine and duloxetine were significantly superior to placebo in the NMA; in addition to these two, agomelatine, imipramine and vortioxetine outperformed placebo in pairwise meta-analyses. Several other drugs were more efficacious than placebo in the secondary efficacy outcomes remission and depressive symptoms. Very limited evidence suggests that competitive memory training, geriatric home treatment group and detached mindfulness condition reduce depressive symptoms in the short term, and collaborative care in the long-term.

It is difficult to compare our results with those of previous publications, because previous reviews focused on special aspects, outcomes and drugs. Nevertheless, the patchwork of previous reviews can be summarized as follows: several meta-analyses showed a significantly greater efficacy of various antidepressants compared to placebo in older adults, although the effect sizes varied (Kok et al., 2012; Mottram et al., 2006; Thorlund et al., 2015; Wilson et al., 2001). In contrast to our NMA, efficacy differences between antidepressants had not been detected in older adults (Gerson et al., 1999; Mittmann et al., 1997; Williams, 2000). Compared to our comprehensive assessment of outcomes, side-effects, quality of life, functioning and other outcomes were incompletely addressed by previous reviews, but TCA were associated with more dropouts in a Cochrane review from 2006 (Mottram et al., 2006). In previous reviews cognitive behavioral therapy was more efficacious than passive control interventions (Kiosses et al., 2011; Peng et al., 2009; Wilson et al., 2008). As none of the included studies in these reviews fulfilled our inclusion criteria, the results are again difficult to compare.

The comprehensive network meta-analysis by Cipriani et al. (2018) is the current gold standard for the comparison of our results with those in younger adults. In contrast to our report all antidepressants examined by Cipriani et al. (2018) were more efficacious than placebo. As many more studies were available (522 RCTs versus 53 RCTs in our report) there is the possibility that if more data become available, more treatments would prove effective in the elderly as well. But in the absence of such data this is a speculation.

We applied specific inclusion criteria suitable for an appropriate definition of the target population, which is particularly important when conducting a network meta-analysis. First, in contrast to other reviews (Kok et al., 2012; Thorlund et al., 2015) which also included younger patients, we decided to only include studies evaluating patients older than 65. In many countries the age of 65 is associated with marked changes in life such as retirement or a loss of close relatives. Moreover, nowadays the physical health of patients in their late 50 s or early 60 s does often not differ from general adults. In order to examine older patients who are clearly different from 'general' adults (usually defined in studies as 18–65 years) who have been extensively examined in other reviews (Cipriani et al., 2018) we therefore focused on an age group which would be classified

as geriatric by recent definitions (Sieber, 2007) including mainly an age of over 70. While such patients are usually excluded from studies in the general population, the mean age in our studies was 73.7 years with a range of 68.9–83.2.

Second, as depressive symptoms can be very different between different types of depression which may lead to differences in treatment effects, we only included patients with a diagnosis of MDD using operationalized criteria.

Finally, we a priori decided in our protocol to only include studies published since 1990. The main reason was that (Furukawa et al., 2016) have shown that placebo response was lower in antidepressant before 1990, while placebo-response remained stable in the subsequent 30 years. The older studies are the more they may also differ in other methodological and patient characteristics. For example, the change in 1993 from DSM-III to DSM-III-R roughly falls in this period (Fountoulakis, 2017). These factors would have potentially violated the transitivity assumption. It should be noted that mainly studies on older antidepressants such as TCAs were affected by this decision and that these drugs are nowadays not commonly used in clinical practice. In summary, we think that if we had included these studies the risk for violating assumptions would overweight the contribution of these studies to the findings.

Due to these strict inclusion criteria, the population of included studies could a priori be assumed to be quite homogeneous, and the results should therefore be considered relevant for patients aged $\geq$65 years with MDD. Nevertheless, we found high statistical inconsistency in the primary outcome 'response to treatment', and depressive symptoms and headache. Inspection of the included trials did not reveal clear reasons for this inconsistency, the trials appeared to be similar and thus transitive. For this reason, we decided to perform a network meta-analysis despite statistical inconsistency. Nevertheless, heterogeneity and inconsistency may explain why some drugs were statistically significantly more efficacious than placebo in pairwise meta-analysis and not in network meta-analysis. For this reason, we downgraded the strength of the evidence in the CINeMA, and recommended cautious interpretation. Moreover, we presented the results of pairwise meta-analysis of these outcomes in the manuscript rather than only in the appendix to emphasize their importance in this situation. Importantly, although in network meta-analysis not all results were statistically significant, the direction of the effect was the same as that in pairwise meta-analysis, making the results complementary. The pattern observed in the secondary efficacy outcomes remission and depressive symptoms was comparable but not identical to that of the primary outcome response to treatment. Such a finding is common in meta-analysis. A frequent reason is that studies do not always report all outcomes. For example, in particular placebo-controlled trials reported "remission" less frequently than "response" (see eAppendix 7). But it is also possible that some drugs improve certain aspects of efficacy more than others.

We extracted all side-effects reported in the primary studies and built groups of similar side effects according to an adapted MedDRA (MedDRA® the Medical Dictionary for Regulatory Activities terminology is the international medical terminology developed under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). MedDRA® trademark is owned by IFPMA on behalf of ICH)approach. This approach led to network meta-analyses for 22, and pairwise meta-analyses for 116 adverse events. This allowed providing a comprehensive picture of the randomised safety data of all available drugs. As safety is of special importance in geriatric patients, this information is highly relevant for clinicians and patients in the decision making process for the best treatment option for individual patients. it should be noted that for some side-effects occasionally there were significantly more events in the placebo group. One interpretation is that these adverse events could be discontinuation effects after abrupt withdrawal of pre-study antidepressant medication (Warner et al., 2006).

This work has limitations. Although we included 53 studies with 9274 participants, the available evidence was limited for some comparisons, especially for non-pharmacological treatments. A frequent reason for exclusion of studies on non-pharmacological interventions was that they did not use operationalised criteria for the diagnosis of MDD. Furthermore, we lost a few studies on older drugs due to the exclusion of studies about pharmacological interventions published before 1990. As explained above, similarity of patient characteristics is critical for the transitivity assumption of NMA which might have been violated. It was not possible to compare pharmacological and non-pharmacological treatments within a network meta-analysis due to missing connection between treatments. As a lot of the included reports were subgroup analysis of larger trials evaluating adult patients, the reporting was insufficient, especially for outcomes such as quality of life and social functioning. Details on methodology such as randomization and allocation concealment methods were also not presented in more than 50% of the included studies which is reflected in the risk of bias ratings and the CINeMA approach. We obtained some unpublished data from authors of included studies. But in the future all data should be made available to make reviews more valid. We undertook a comprehensive literature search, but we could not formally test for publication bias and it is known that publication bias exists in this area (Turner et al., 2008). As mentioned by a reviewer a general problem of meta-analytical methods is that they summarize results from primary studies, that they allow statements about probabilities and risks, and that they can generate hypotheses, but that strictly speaking they cannot empirically test a hypothesis. An empirical test is only possible in a prospective, randomized, double-blind study." Finally, it should be noted that quetiapine is only approved as a monotherapy in depression in the context of bipolar disorder, while in unipolar depression it is only approved as an augmentation strategy. To use it in monotherapy for major depressive disorder means off-label use.

Our review has several implications for clinical practice, regulatory issues, and research-related issues. In terms of clinical practice our review provides a comprehensive evaluation of efficacy and hundred-sixteen adverse events, which allows an improvement of the individualised decision making process in patients with MDD. In terms of research we showed that the evidence for non-pharmacological treatments as well as the evidence for most of the antidepressants is still scarce and more studies in this population are needed. We suggest a better reporting of important

characteristics (e.g. comorbidities, polypharmacy) in the primary studies. Our results provide also information that can have an impact in terms of regulatory issues. Interestingly quetiapine, a drug which was originally developed as an antipsychotic, was among the most efficacious drugs.

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Contributors

SL received the funding and supervised the work. MK and SL designed the study. MK, KG and SL assessed the studies. MK and KG extracted the data. JS and MK created the Access database. AC and MK analysed the data. KG, IB and MK drew the tables and figures. MK, KG, and SL interpreted data. MK, IB and SL wrote the first draft of the manuscript and all authors contributed to and have approved the final version.

Declaration of interests

SL has received honoraria for consulting from LB Pharma, Lundbeck, Otsuka, TEVA, Geodon Richter, Recordati, LTS Lohmann, and Boehringer Ingelheim; and for lectures from Janssen, Lilly, Lundbeck, Otsuka, SanofiAventis, and Servier. All other authors declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2019.07.130.

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