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Updates in treating major depressive disorder in the elderly: a systematic review

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Summary

Among mental disorders, late life depression occurs in 7% of the general older population.

An updated systematic review of randomized controlled trials (RCTs) on pharmacological and non-pharmacological treatment of major depressive disorder (MDD) in the elderly was conducted.

Eight RCTs were carried out on 663 patients (mean age 70.99, SD 6.73). Vortioxetine (p = 0.897), saffron (η^2 = 0.008) and tianeptine (p = 0.32) reduced depressive symptoms in MDD older adults, although no significant differences in their efficacy were found when compared to sertraline and escitalopram, respectively. Focusing on adverse events, in comparison with sertraline, vortioxetine did not show any significantly difference, while saffron was associated to less neurological disorders (RR 0.13, 95% CI 0.17-0.93, p = 0.02). Neurological (RR 0.46, 95% CI 0.3-0.71, p = 0.000) and gastrointestinal (RR 0.54, 95% CI 0.31-0.96, p = 0.04) disorders were also less common in patients under tianeptine compared to escitalopram.

Although significant effects for some pharmacological and non-pharmacological interventions in older patients, the overall MDD evidence is still scant and more studies are needed in this vulnerable segment of population.

Key words: elderly, major depressive disorder, treatment

Introduction

The world's population is ageing rapidly. As reported by the World Health Organization (WHO), between 2015 and 2050, the proportion of the world's older adults is estimated to almost double from about 12% to 22% [1]. Older adults make important contributions to society as family members, volunteers and as active participants in the workforce. The protection of the physical and mental health status of this vulnerable segment of population needs to be recognized as a real public health priority [2].

Among mental disorders, late life depression occurs in 7% of the general older population and accounts for 5.7% of Years Lived with Disability (YLDs) among those over 60 years old 1. Diagnosing depression in older adults can be more difficult than in young people because of physical comorbidities and cognitive dysfunction [3,4]. Depressive symptoms are often overlooked and untreated and they are accompanied by poorer functioning compared to chronic medical conditions [5,6]. Moreover, depression can increase the perception of poor health, the utilization of health care services and costs, as well as the burden on their families and caregivers [7].

There is no single preferred intervention for depression in older adults, and a wide variety of treatments can be used [8]. Findings from a systematic re-

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The manuscript has been approved by all authors. Studies were identified and independently reviewed for eligibility by the two authors (Amerio, Aguglia) in a two-step based process. Data were extracted by one author (Amerio) and supervised by a second author (Serafini) using an ad-hoc developed data extraction spreadsheet. Our manuscript has been approved by all authors.

view conducted in 2017 by Krause and colleagues on randomized controlled trials (RCTs) revealed several antidepressants and quetiapine to be efficacious in elderly patients with major depressive disorder (MDD), but due to the comparably few available data, results were not robust [9]. Moreover, although significant effects were found for some non-pharmacological treatments, the overall evidence was insufficient, because of based on a few trials with small sample sizes [10].

Aim of the study

We updated Krause and colleagues' systematic review of all RCTs on pharmacological and non-pharmacological treatment of MDD in the elderly to provide recommendations for clinical management and future research.

Methods

Information sources and search strategy

This systematic review was conducted according to methods recommended by the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11,12]. Studies were identified searching the electronic databases MEDLINE, Embase, PyscInfo, CINAHL, ClinicalTrials.gov, Web of Science, and the Cochrane Library. We combined free text terms and MeSH heading as described in Appendix 1. As done before [13,14], the strategy was first developed in MEDLINE and then adapted for use in the other databases. Studies in English published from December 12th, 2017 to January 1st, 2021 were included. In addition, further studies were retrieved from reference listing of relevant articles and consultation with experts in the field.

Study population and study designs

We searched for RCTs carried out in elderly patients with a primary diagnosis of major depressive disorder. The diagnosis was made according to the Diagnostic and Statistical Manual (DSM) criteria for major depressive disorder, or the International Statistical Classification of Diseases (ICD-10) criteria for recurrent depressive disorder. Studies using other diagnostic criteria were excluded. However, as done previously [9], given the variety of depressive forms, studies were accepted if less than 20% of population had another form of depression. Studies of relapse prevention carried out in non-acute patients were excluded.

Interventions

Pharmacological and non-pharmacological interventions, such as psychotherapy and physical activity, were included. Active controls were allowed as well as placebo. Due to either scarce clinical relevance for the elderly and the risk of confounding factors, we excluded studies of combination therapy.

Outcomes

The number of patients responding to treatment was the main outcome, defined as a score reduction of at least 50% from baseline to endpoint or follow-up on a validated scale. In addition, remission of symptoms was defined as: 7 or less on the 17-item Hamilton Depression Rating Scale (HDRS); 8 or less for longer versions of HDRS; 6 or less on the Montgomery-Asberg-Depression Scale (MADRS); 10 or less on the Beck Depression Inventory (BDI); 5 or less on the Geriatric Depression scale (GDS). The mean reduction of depressive symptoms from baseline to the endpoint was also investigated. Moreover, the incidence and main causes of adverse events were included as outcomes of primary interest, as well as dropouts, deaths, and suicides.

Study selection and data extraction

Identified studies were independently reviewed for eligibility by the two authors (MA, AA) in a two-step process: a first screening was performed based on titles and abstracts, then full texts were retrieved for a second screening. Disagreement was resolved by consensus. Data were extracted using an ad-hoc developed data extraction spreadsheet.

Data items

Information was extracted from each included study on: 1) study design, time and country of intervention, sample size, study arms; 2) age, sex and comorbidities of participants; 3) type, name, dose and duration of interventions and controls; 4) name of rating scales, baseline and completion mean rating scores in study groups, Relative Risks (RRs) of response to treatment and symptom remission; 5) frequencies and descriptions of adverse events and dropouts.

Quality assessment

The revised Cochrane risk of bias tool for randomized trials (RoB 2) was used to assess the risk of bias in individual studies [15].

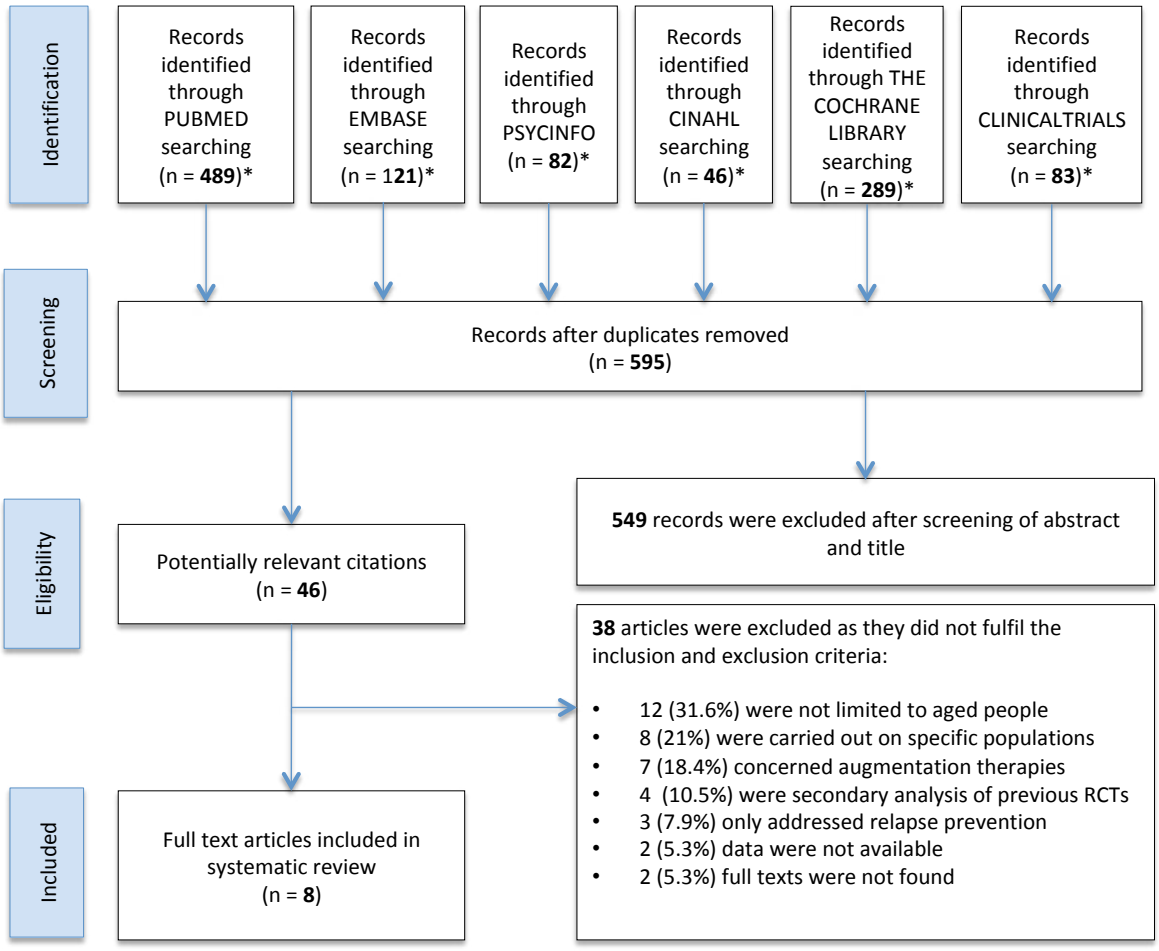
Results

Study selection

Six hundred eighty potential studies were identified from the selected databases and after cross-checking references of relevant articles. Five hundred ninety-five studies were retrieved after duplicate removal. Studies were screened and selected as described in Figure 1. Eight RCTs were included in the systematic review.

Study characteristics and populations

Characteristics of included studies are reported in Table I. All the studies were RCTs and half were double-blind-



** Search strategy limited from December 12th, 2017 to January 1st, 2021, English language, human subjects, aged 65 or more.*

Figure 1. Flow diagram of selected articles.

ed [16-19]. All the trials were two-armed except for one three-armed RCT [18]. The study sample sizes ranged from 20 to 311 patients, with a total sample size of 663.

Three studies (37.5%) were carried out in North America 19-21, two (25%) in the Middle East [16,17], one (12.5%) in Asia [22] and one in Europe [23]. The remaining trial was conducted in different centers of Europe, Asia, and America [18]. The mean age ranged from 68.85 ± 6.16 to 88.3 ± 5.3 [20,23]. The combined mean age of the review was 70.99 ± 6.73.

One trial was entirely carried out on men [23]. The rate of females in the remaining studies ranged from 30% [16] to 74.36% [22]. The overall female rate of the review was 64.71%.

Participants of all studies were included based on an objective diagnosis. DSM-5 was used by three (37.5%) studies [16,17,19], while the fourth edition was used by two (25%) [18,21]. Three studies (37.5%) reported using the Structured Clinical Interview for either DSM-IV or DSM-5 [17,19,21]. One study (12.5%) used the Mini-International Neuropsychiatric Interview (MINI) [22]. The remaining two studies (25%) reported a diagnostic score on respectively the 17-item HDRS [20] and the GDS [23].

Pharmacological interventions

As shown in Table II, pharmacological treatments were studied by four RCTs (50%), accounting for 450 (67.87%) of the overall patients in review. Saffron [16], vortioxetine [17], tianeptine [18], and levomilnacipran [19] were investigated. Sertraline, at mean doses of 100 and 75 mg/die respectively, was used as an active control in two studies [16,17]. One trial was placebo-controlled [19], while another one adopted both placebo and active control with escitalopram 10 mg/die [18]. Interventions were completed after six [16,17], eight [18] or twelve weeks [19].

Non-pharmacological interventions

Four studies (50%) performed non-pharmacological interventions, accounting for about 32.13% out of the review overall sample size [20-23].

Two trials (25%) performed different types of reward-based psychotherapies and multidomain interventions [21,22]. Both trials performed psychotherapy-based controls. One study (12.5%) reported an intervention consisted in a 10-min-

Table I. Study populations and characteristics.

Author	Year	Country	Study Design	Study Arms	Sample Size			Age	Female Rate		Diagnostic criteria	Risk of bias*
					Tot.	Treat.	Ctrl.					
					n	n (%)	n (%)	mean,SD	n	%		
Ahmadpanah et al. [16]	2019	Iran	DB-RCT	2	50	25	25	65.6, 4.32	15	30.00%	DSM-5	Low
Borhannejad et al. [17]	2020	Iran	DB-RCT	2	60	30	30	70.64, 8.26	37	61.67%	SCID (DSM-5)	Low
Emsley et al. [18]	2018	Multi-center	DB-RCT	3	311	105	107 (placebo)	70.44, 4.78	225	72.35%	DSM-IV-TR	Low
							99 (escit.)					
Ionson et al. [20]	2018	Canada	RCT	2	83	40	43	68.85, 6.16	57	68.67%	HRSD-17	High
Krause-Sorio et al. [19]	2019	USA	DB-RCT	2	29	17	12	71.52, 5.79	14	48.28%	SCID (DSM-5)	High
Roh et al. [22]	2019	Korea	RCT	2	78	38	40	74.0, 5.8	58	74.36%	MINI	Low
Solomonov et al. [21]	2020	USA	RCT	2	32	16	16	72.35, 8.12	23	71.88%	SCID (DSM-IV)	Some concerns
Verrusio et al. [23]	2018	Italy	RCT	2	20	10	10	88.3, 5.3	0	0%	GDS	Some concerns

*DB-RCT: Double-Blind Randomized Controlled Trial; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth edition; SCID: Structured Clinical Interview for DSM; HRSD-17: 17-item Hamilton Depression Rating Scale; MINI: Mini-International Neuropsychiatric Interview; GDS: Geriatric Depression Scale. * Summary evaluation according to the revised Cochrane risk of bias tool for randomized controlled trials.*

utes phone call per week and 60-minutes home visits every four weeks [22].
One study (12.5%) carried out one session per week of meditation practices. Sessions lasted 60 minutes. The trial was controlled by treatment as usual consisting in antidepressants and supportive psychotherapy [20].
The last study [23] performed three 45-minutes sessions of physical activity per week, with use of Human Body Posturizers (HBPs) in the treatment group.
Trials were completed after either nine [22], twelve [20] or twenty four [21,23] weeks.

Outcome measurement

Six studies (75%) rated the variations of symptoms with the HDRS, either in its 17-item [16-18,20] or 24-item versions [19,21] (Table III). The last two studies adopted the MADRS [22] and the GDS [23], respectively.

Treatment response, remission and reduction of symptoms

We were able to determine the effect sizes and significance levels for treatment response and symptom remission of four (50%) pharmacological [16-19] and one (12.5%) non-pharmacological interventions [20].
With regard to pharmacological RCTs, the comparisons of saffron [13] and vortioxetine [14] with sertraline were not different for reduction of depressive symptoms ($\eta^2 = 0.008$ and $p = 0.897$, respectively). Symptom reduction was as well no significantly different between tianeptine and escitalopram ($p = 0.32$) [15]. Vortioxetine showed no significant difference with sertraline in treatment response (RR 1.02, 95% CI 0.67-1.55, $p = 1.00$) [17]. Differences in remission probability for saffron (RR 1.0, 95% CI 0.61-1.63, $p = 1$) [16] and vortioxetine (RR 0.6, 95% CI 0.25-1.44, $p = 0.38$) [17] compared to sertraline had a poor statistical significance. Levomilnacipran had no significant effect on remission compared to placebo (RR 1.41, 95% CI 0.31-6.51, $p = 1$) [19].
In one non-pharmacological RCT, meditation practice showed a small effect size and little significance level for response (RR 2.58, 95% CI 1.00-6.67, $p = 0.06$), whereas remission rates were consistently higher in the control group rather than the intervention group (RR 0.24, 95% CI 0.05-0.42, $p = 0.03$) [20].
Multidomain intervention showed a significant reduction of depressive symptoms compared to supportive therapy (score difference: 5.117, $p = 0.029$) [22]. One intervention of reward-based psychotherapy reduced the symptoms as well as problem-solving therapy in control group ($p < 0.0001$) [21]. Physical activity with HBPs significantly contributed to depressive symptom reduction compared to classic physical exercise ($p = 0.01$) [23].

Table II. Characteristics of interventions

Author	Year	Sample Size			Study Duration	Treatment		Control	
		Tot.	Treat.	Ctrl.		Name	Characteristics	Name	Characteristics
		N	N. (%)	N. (%)	Weeks				
2.1. RCTs of pharmacological interventions									
Ahmadpanah et al. [16]	2019	50	25	25	6	Saffron (C. Sativus L.)	60 mg/die	Sertraline	100 mg/die
Borhannejad et al. [17]	2020	60	30	30	6	Vortioxetine	15 mg/die	Sertraline	75 mg/die
Emsley et al. [18]	2018	311	105	107	8	Tianeptine	50 mg/die	Placebo	
				99				Escitalopram	10 mg/die
Krause-Sorio et al. [19]	2019	29	17	12	12	Levomilnacipran	40 (20-120) mg/die	Placebo	NA
2.2. RCTs of non-pharmacological interventions									
Ionson et al. [20]	2018	83	40	43	12	Sahaj Samadi meditation	60 min 1/week	Treatment as usual	antidepressants supportive psychotherapy
Roh et al. [22]	2019	78	38	40	9	"Gold Medal Program" multidomain intervention	10-min phone call: 1/week 60-min visit: 1/month	Supportive therapy	10-min phone call: 1/week 60-min visit: 1/month
Solomonov et al. [21]	2020	32	16	16	24	"Engage" psychotherapy	NA	Problem-solving therapy	NA
Verrusio et al. [23]	2018	20	10	10	24	Physical activity with Human Body Posturizer (HBP)	45 min 3/week	Physical exercise training	45 min 3 sessions/week

NA: Not Available

Dropouts and adverse events

Attrition rates of five (62.5%) studies [16-20] ranged from 11.25% [18] to 51.72% [19] (Table III). The effect size for dropouts due to adverse events in treatment compared to placebo was high in one RCT, with strong inconsistence (RR 5.38, 95% CI 0.66-44.04, p = 0.1) [20].

The effect sizes and significance levels of adverse events were drawn out for the pharmacological interventions [16-19] (Table IV). The adverse events reported in the RCTs were allocated to six categories: gastrointestinal, cardiovascular, respiratory, neurological, psychiatric, and sleep disorders. Three trials (37.5%) reported significant results for neurological disorders. Neurological adverse events were less frequent in saffron than sertraline (RR 0.13, 95% CI 0.17-0.93, p = 0.02) [16]. Levomilnacipran was consistently related to adverse neurological events in one placebo-controlled RCT (RR 12, 95% CI 1.84-78.37, p = 0.000) [19]. Neurological (RR 0.46, 95% CI 0.3-0.71, p = 0.000) and gastrointestinal (RR 0.54, 95% CI 0.31-0.96, p = 0.04) disorders were less common in tianeptine than escitalopram users [18].

Risk of bias

A high risk of bias was assessed for two studies (25%) [19,20], whereas two other studies 21,23 presented some concerns of bias risk in RoB-2 assessment. However, the risk of bias was low in three (37.5%) pharmacological [16-18] and one (12.5%) non-pharmacological interventions [22], respectively.

Discussion

An update of Krause and colleagues' systematic review [9] of all pharmacological and non-pharmacological RCTs published in recent years in the treatment of MDD in the elderly was conducted. With regard to pharmacological interventions, both vortioxetine, saffron and tianeptine reduced depressive simptoms in MDD older adults, although no significant differences in their efficacy were

Table III. Efficacy and dropouts.

Author	Intervention	Rating scale	Scores at Baseline		Scores at Completion		Response		Remission		Attrition rate	Dopouts due to adverse events	
			Treatment	Control	Treatment	Control							
			Mean, SD	Mean, SD	Mean, SD	Mean, SD	RR (95% CI)	P*	RR (95% CI)	P*	%	RR (95% CI)	P*
Ahmadpanah et al. [16]	Saffron (C. Sativus L.)	HRSD-17	21.12, 2.35	21.4, 2.86	9.92, 4.51	8.76, 4.52	8 (1.08 -59.32)	0.02	1.0 (0.61-1.63)	1.00	16,00%	0	0.49
Borhannejad et al. [17]	Vortioxetine	HRSD-17	30.6, 4.07	30.88, 5.93	21.52, 4.79	21.96, 6.1	1.02 (0.67-1.55)	1.00	0.6 (0.25-1.44)	0.38	16,67%	NA	NA
Emsley et al. [18]	Tianeptine	HRSD-17	26.7, 3.2	26.6, 3.5 (placebo)	13.3, 7.0	17.1, 6.9 (placebo)	1.39 (0.99-1.94)	0.07	NA	NA	11,25%	0.51 (0.13-1.98)	0.50
				26.7, 3.2 (escitalopram)		13.1, 6.6 (escitalopram)	0.86 (0.65-1.12)	0.27	NA	NA	NA	0.47 (0.12-1.83)	0.32
Krause-Sorio et al. [19]	Levomilnacipran	HRSD-24	NA	NA	NA	NA	NA	NA	1.41 (0.31-6.51)	1.00	51,72%	-	0.12
Ionson et al. [20]	Sahaj Samadi meditation	HRSD-17	14.16, 4.1	15.2, 4.4	NA	NA	2.58 (1.00-6.67)	0.06	0.24 (0.05-0.42)	0.03	15,66%	5.38 (0.66-44.04)	0.1
Roh et al. [22]	"Gold Medal Program" multidomain intervention	K-MADRS	31.6, 9.0	31.9, 7.9	NA	NA	NA	NA	NA	NA	NA	NA	NA
Solomonov et al. [21]	"Engage" psychotherapy	HRSD-24	22.9, 4.29	22.2, 4.45	NA	NA	NA	NA	NA	NA	NA	NA	NA
Verrusio et al. [23]	Physical activity with Human Body Posturizer (HBP)	GDS	8.5, 1.17	8.6, 1.26	5.2, 1.1	7.9, 1.0	NA	NA	NA	NA	NA	NA	NA

*HRSD -17 (24): 17 (24)-item version of Hamilton Rating Scale for Depression; K-MADRS: Korean version of Montgomery-Asberg Depression Rating Scale; GDS: Geriatric Depression Scale. *P: Two-sided Fisher's exact P. NA: Not Available.*

found when compared to sertraline and escitalopram, respectively. Focusing on adverse events, in comparison with sertraline, vortioxetine did not show any significantly difference, while saffron was associated to less neurological disorders. Neurological and gastrointestinal disorders were also less common in patients under tianeptine compared to escitalopram. Considering non-pharmacological interventions, response rates for one meditation-based trial were slightly higher than treatment as usual, but estimates had a poor consistence. Multi-domain intervention, reward-based psychotherapy and physical activity with HBP significantly reduced depressive symptoms in older patients compared to control groups.

In terms of response to treatment, Krause and colleagues' network-meta-analysis [9] showed a significant superiority for quetiapine and duloxetine compared to placebo [24]. Moreover, 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 [9]. With regard to non-pharmacological interventions, very limited evidence suggested that competitive memory training, geriatric home treatment group and detached mindfulness condition reduced depressive symptoms.

The small number of selected RCTs analizing different type of pharmacological interventions (except vortioxetine), does not allow a comparison with the results of the previous systematic review either in terms of efficacy or safety. Antidepressants keep to be effective in decreasing depressive symptoms in the elderly showing a significant superiority compared to placebo without, however, significant differences in comparison to controls (sertraline and escitalopram, respectively). Insufficient and not robust evidence supports the use of non-pharmacological approaches in treating MDD older patients.

Table IV. Adverse events.

	Intervention/ Control	Gastrointestinal disorders			Cardiovascular disorders			Respiratory disorders			Neurological disorders			Psychiatric disorders			Sleep Disorders		
		RR	95% CI	P*	RR	95% CI	P*	RR	95% CI	P*	RR	95% CI	P*	RR	95% CI	P*	RR	95% CI	P*
Ahmadpanah et al. [16]	Saffron/ Sertraline	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.13	0.17-0.93	0.02	NA	NA	NA	0	NA	0.49
Borhannejad et al. [17]	Vortioxetine/ Sertraline	0.82	-0.33-0.2	0.76	0.5	0.05-5.22	1	NA	NA	NA	1	0.07-15.26	1	NA	NA	NA	0.4	0.14-1.14	0.13
Krause-Sorio et al. [9]	Levomilnacipran/ Placebo	NA	NA	0.023	1.76	0.41-7.63	0.66	NA	NA	NA	12	1.84-78.37	0.000	NA	NA	NA	0.06	-0.05-0.17	1
Emsley et al. [18]	Tianeptine/ Placebo	0.85	0.45-1.59	0.71	NA	NA	NA	1.02	0.06-16.08	1	0.86	0.53-1.42	0.62	1.02	0.15-7.1	1	1.02	0.65-16.08	1
	Tianeptine/ Escitalopram	0.54	0.31-0.96	0.04	0		0.23	0.47	0.43-5.12	0.61	0.46	0.3-0.71	0.0003	0.31	0.06-1.52	0.16	0.31	0.03-2.97	0.36

NA: Not Available.

Along to the efficacy, particularly in older patients, differences in side-effects should be considered in drug choice. Feeling reluctant to use synthetic drugs frequently induce the elderly to take herbal products [25]. Above all, saffron has been already succesfully used for depressive symptoms [26] along to several somatic complaints, such as premenstrual syndrome, post-menopausal flashes, sexual dysfunction and infertility, and excessive snacking behaviors 27. The relatively low efficacy showed by antidepressants – only one out of nine people benefit from them [27] – and the risk of unnecessarily side effects, could increase attraction for herbal products, including saffron, in the older people.

This systematic review needs to be interpreted in the light of several strengths and limitations. Only RCTs were included and their quality was evaluated using a widely recognized tool for bias risk assessment. Most of the RCTs carefully reported study procedures and methodology. The scarce number of included studies reflects the selectivity of our inclusion and exclusion criteria. Study power was thoroughly affected by the short sample sizes. Consistent results were scant, and the effect sizes were often low. Some studies were at high risk of bias (Table I) and, not always, efficacy was the major outcome of the trials, raising concerns on selection bias risk [19].

The WHO proposition that there can be “no health without mental health” [28] is valid for everybody, but even more so for fragile groups, as the elderly, because of medical comorbidities, cognitive dysfunctions and polypharmacotherapies. Although significant effects for some pharmacological and non-pharmacological interventions in older patients, the overall MDD evidence is still scant and not robust. Further studies are needed in this vulnerable segment of population to confirm or refute our findings and consequent clinical recommendations [29].

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Appendix 1. MEDLINE Search Strategy.

SET	MEDLINE
1	Elder* OR old OR older OR "senior citizen" OR Aging OR aged OR "late-life" OR "late life" OR "late adult*" OR "late-adult*"
2	geriatri* OR geronto* OR psychoger* or geropsych*
3	older AND (65 OR 70 OR 75 OR 79 OR 80 OR 85 OR 90 OR 95) AND years
4	*Aged*
5	*Health Services for the Aged*
6	*Health Services for the Elderly*
7	Sets 1-6 were combined with "OR"
8	Depress* OR "unipolar depression" OR "major depressive disorder" OR MDD
9	(affective OR mood) AND (symptom* OR disorder*)
10	"Beck Depression Inventory" OR BDI OR Hamilton OR HAM-D OR "Montgomery-Asberg Depression Rating Scale" OR MADRS OR "Geriatric Depression Scale" OR GDS OR "depression rating scale" OR (operationali* AND diagnosis)
11	"ICD-10" AND "F33*"
12	*Depression*
13	*Depressive disorder*
14	*Depressive disorder, Major*
15	Sets 8-14 were combined with "OR"
16	antidepress* OR "anti depress*" OR MAOI* OR "monoamine oxidase inhibit*" OR ((serotonin OR norepinephrine OR noradrenaline OR "nor epinephrine" OR "nor adrenaline" OR neurotransmitt* OR dopamine*) AND (uptake OR reuptake OR re-uptake)) OR noradrenerg* OR antiadrenergic OR "anti adrenergic" OR SSRI* OR SNRI* OR TCA* OR tricyclic* OR tetracyclic* OR heterocyclic* OR psychotropic* Agomelatine OR Alaproclate OR Amoxapine OR Amineptine OR Amitriptylin* OR Amitriptylinoxide OR Atomoxetine OR Befloxatone OR Benactyzine OR Binospirone OR Brofaromine OR (Buproprion OR Amfebutamone) OR Butriptyline OR Caroxazone OR Cianopramine OR Cilobamine OR Cimoxatone OR Citalopram OR (Chlorimipramin* OR Clomipramin* OR Chlomipramin* OR Clomipramine) OR Clorgyline OR Clovoxamine OR (CX157 OR Tyrima) OR Demexiptiline OR Deprenyl OR (Desipramine* OR Pertofrane) OR Desvenlafaxine OR Dibenzepin OR Diclofensine OR Dimetacrin* OR Dosulepin OR Dothiepin OR Doxepin OR Duloxetine OR Desvenlafaxine OR DVS-233 OR Escitalopram OR Etoperidone OR Femoxetine OR Fluotracen OR Fluoxetine OR Fluvoxamine OR (Hyperforin OR Hypericum OR St John*) OR Imipramin* OR Iprindole OR Iproniazid* OR Ipsapirone OR Isocarboxazid* OR Levomilnacipran OR Lofepramine* OR ("Lu AA21004" OR Vortioxetine) OR "Lu AA24530" OR (LY2216684 OR Edivoxetine) OR Maprotiline OR Melitracen OR Metapramine OR Mianserin OR Milnacipran OR Minaprine OR Mirtazapine OR Moclobemide OR Nefazodone OR Nialamide OR Nitroxazepine OR Nomifensine OR Norfenfluramine OR nortriptylin* OR Noxiptilin* OR Opipramol OR Oxaflozane OR Paroxetine OR Phenelzine OR Pheniprazine OR Pipofezine OR Pirlindole OR Pivagabine OR Pizotyline OR Propizepine OR Protriptylin* OR Quinupramine OR Reboxetine OR Rolipram OR Scopolamine OR Selegiline OR Sertraline OR Setiptiline OR Teciptiline OR Thozalinone OR Tianeptin* OR Toloxatone OR Tranylcypromin* OR Trazodone OR Trimipramine OR Venlafaxine OR Viloxazine OR Vilazodone OR Viqualine OR Zalospirone
17	*Antidepressive Agents*
18	*Antidepressive Agents, Tricyclic*
19	*Adrenergic Uptake Inhibitors*
20	*Psychotropic Drugs*
21	*Monoamine Oxidase Inhibitors*
22	*Serotonin and Noradrenaline Reuptake Inhibitors*
23	sets 16-22 were combined with "OR"
24	Psychotherapy
25	Cognitive therapy
26	Behavioral therapy
27	Dynamic therapy
28	Collaborative care
29	Physical exercise
30	*Psychotherapy*
31	sets 24-30 were combined with "OR"
32	sets 23 and 31 were combined with "OR"
33	sets 7, 15, 32 were combined with "AND"
34	set 33 was limited from December 17th, 2017 to January 1st, 2021; English language; Aged: > 65 years; Study design: Randomized Controlled Trials (RCTs)