

Table S1 Search strategy in five different databases

Databases and search terms				
PubMed	Cochrane	PsycINFO	LILACS	Embase
(("Obsessive-Compulsive Disorder"[Title/Abstract] OR "Compulsive Behavior"[Title/Abstract] OR "obsession"[Title/Abstract] OR "obsessional"[Title/Abstract] OR "obsessions"[Title/Abstract] OR "obsessive"[Title/Abstract] OR "compulsion"[Title/Abstract] OR "compulsions"[Title/Abstract] OR "compulsive"[Title/Abstract]) AND ("drug therapy"[Title/Abstract] OR "serotonin reuptake inhibitors"[Title/Abstract] OR "clomipramine"[Title/Abstract] OR "Serotonin and Noradrenaline Reuptake Inhibitors"[Title/Abstract] OR "Antipsychotic Agents"[Title/Abstract] OR "Excitatory Amino Acid Agents"[MeSH Terms] OR "Antipsychotic Agents"[MeSH Terms] OR "agents glutamate"[Title/Abstract] OR "agents glutamatergic"[Title/Abstract] OR "Topiramate"[Title/Abstract] OR "Memantine"[Title/Abstract] OR "Acetylcysteine"[Title/Abstract] OR "Lamotrigine"[Title/Abstract] OR "Ketamine"[Title/Abstract]) AND	#1 (Obsessive-Compulsive Disorder):ti,ab,kw OR (Compulsive Behavior):ti,ab,kw OR (obses*):ti,ab,kw OR (compuls*):ti,ab,kw #2 (drug therapy OR clomipramine OR ssri OR selective serotonin reuptake inhibitor OR fluoxetine OR escitalopram OR citalopram OR fluvoxamine OR sertraline OR paroxetine OR Serotonin and Noradrenaline Reuptake Inhibitors OR venlafaxine OR desvenlafaxine OR duloxetine OR antipsychotics OR memantine OR lamotrigine OR ketamine OR Acetylcysteine OR topiramate):ti,ab,kw #3 MeSH descriptor: [Antipsychotic Agents] explode all trees #4 MeSH descriptor: [Excitatory Amino Acid Agents] explode all trees #5 #2 OR #3 OR #4 #6 #1 AND #5 with	((title: ("Obsessive-Compulsive Disorder") OR title: ("Compulsive Behavior") OR title: (obses*) OR title: (compuls*) OR (abstract: ("Obsessive-Compulsive Disorder") OR abstract: ("Compulsive Behavior") OR abstract: (obses*) OR abstract: (compuls*)) AND ((title: ("drug therapy") OR title: (clomipramine) OR title: (ssri) OR title: ("selective serotonin reuptake inhibitor") OR title: (fluoxetine) OR title: (escitalopram) OR title: (citalopram) OR title: (fluvoxamine) OR title: (sertraline) OR title: (paroxetine) OR title: ("Serotonin and Noradrenaline Reuptake Inhibitors") OR title: (venlafaxine) OR title: (desvenlafaxine) OR title: (duloxetine) OR title: (antipsychotics) OR title: (Neuroleptic Drugs) OR title: (memantine) OR title: (lamotrigine) OR title: (ketamine) OR title: (Acetylcysteine) OR title: (topiramate)) OR (abstract:	((((ti:("obsessive-compulsive disorder")) OR (ti:("compulsive behavior")) OR (ti:(obses*)) OR (ti:(compuls*)) OR (ab:("obsessive-compulsive disorder")) OR (ab:("compulsive behavior")) OR (ab:(obses*)) OR (ab:(compuls*)) AND ((ti:(drug therapy)) OR (ti:(clomipramine)) OR (ti:(ssri)) OR (ti:(selective serotonin reuptake inhibitor)) OR (ti:(fluoxetine)) OR (ti:(escitalopram)) OR (ti:(citalopram)) OR (ti:(fluvoxamine)) OR (ti:(sertraline)) OR (ti:(paroxetine)) OR (ti:(serotonin AND noradrenaline reuptake inhibitors)) OR (ti:(venlafaxine)) OR (ti:(desvenlafaxine)) OR (ti:(duloxetine)) OR (ti:(antipsychotics)) OR (ti:(memantine)) OR (ti:(lamotrigine)) OR (ti:(ketamine)) OR (ti:(acetylcysteine)) OR (ti:(topiramate))) OR ((ab:(drug therapy)) OR (ab:(clomipramine)) OR (ab:(ssri)) OR (ab:(selective	((('obsessive compulsive disorder':ab,ti OR 'obsession':ab,ti OR 'compulsion':ab,ti) AND ('drug therapy':ab,ti OR 'serotonin uptake inhibitor':ab,ti OR fluoxetine:ab,ti OR 'fluvoxamine':ab,ti OR 'fluvoxamine maleate':ab,ti OR sertraline:ab,ti OR paroxetine:ab,ti OR escitalopram:ab,ti OR citalopram:ab,ti OR clomipramine:ab,ti OR 'neuroleptic agent':ab,ti OR 'neuroleptic agent'/exp OR 'serotonin noradrenalin reuptake inhibitor':ab,ti OR venlafaxine:ab,ti OR desvenlafaxine:ab,ti OR duloxetine:ab,ti OR memantine:ab,ti OR topiramate:ab,ti OR lamotrigine:ab,ti OR ketamine:ab,ti OR acetylcysteine:ab,ti)) AND ((2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py OR 2020:py) AND ([adult]/lim OR [aged]/lim))

Databases and search terms				
PubMed	Cochrane	PsycINFO	LILACS	Embase
2013/01/01:2020/12/31[Date - Publication]) AND (alladult[Filter])	Cochrane Library publication date Between Jan 2013 and Dec 2020, in Cochrane Reviews, Cochrane Protocols and Trials	("drug therapy") OR abstract: (clomipramine) OR abstract: (ssri) OR abstract: ("selective serotonin reuptake inhibitor") OR abstract: (fluoxetine) OR abstract: (escitalopram) OR abstract: (citalopram) OR abstract: (fluvoxamine) OR abstract: (sertraline) OR abstract: (paroxetine) OR abstract: ("Serotonin and Noradrenaline Reuptake Inhibitors") OR abstract: (venlafaxine) OR abstract: (desvenlafaxine) OR abstract: (duloxetine) OR abstract: (antipsychotics) OR abstract: (Neuroleptic Drugs) OR abstract: (memantine) OR abstract: (lamotrigine) OR abstract: (ketamine) OR abstract: (Acetylcysteine) OR abstract: (topiramate)) OR (MeSH: (Antipsychotic Agents)) OR (MeSH: (Excitatory Amino Acid Agents))) AND Age Group: Adulthood (18 yrs & older) AND Year: 2013 To 2020	serotonin reuptake inhibitor)) OR (ab:(fluoxetine)) OR (ab:(escitalopram)) OR (ab:(citalopram)) OR (ab:(fluvoxamine)) OR (ab:(sertraline)) OR (ab:(paroxetine)) OR (ab:(serotonin AND noradrenaline reuptake inhibitors)) OR (ab:(venlafaxine)) OR (ab:(desvenlafaxine)) OR (ab:(duloxetine)) OR (ab:(antipsychotics)) OR (ab:(memantine)) OR (ab:(lamotrigine)) OR (ab:(ketamine)) OR (ab:(acetylcysteine)) OR (ab:(topiramate))) OR (mh:(antipsychotic agents)) OR (mh:(excitatory amino acid agents))) AND (db:("LILACS"))	disorder':ab,ti OR 'obsession':ab,ti OR 'compulsion':ab,ti) AND ('drug therapy':ab,ti OR 'serotonin uptake inhibitor':ab,ti OR fluoxetine:ab,ti OR 'fluvoxamine':ab,ti OR 'fluvoxamine maleate':ab,ti OR sertraline:ab,ti OR paroxetine:ab,ti OR escitalopram:ab,ti OR citalopram:ab,ti OR clomipramine:ab,ti OR 'neuroleptic agent':ab,ti OR 'neuroleptic agent'/exp OR 'serotonin noradrenalin reuptake inhibitor':ab,ti OR venlafaxine:ab,ti OR desvenlafaxine:ab,ti OR duloxetine:ab,ti OR memantine:ab,ti OR topiramate:ab,ti OR lamotrigine:ab,ti OR ketamine:ab,ti OR acetylcysteine:ab,ti)) AND ((1966:py OR 1967:py OR 1968:py OR 1969:py OR 1970:py OR 1971:py OR 1972:py OR 1973:py OR 1974:py OR 1975:py OR 1976:py OR 1977:py OR 1978:py OR 1979:py OR 1980:py OR 1981:py OR 1982:py OR 1983:py OR 1984:py OR 1985:py OR 1986:py OR 1987:py OR 1988:py OR 1989:py OR

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				1990:py OR 1991:py OR 1992:py OR 1993:py OR 1994:py OR 1995:py OR 1996:py OR 1997:py OR 1998:py OR 1999:py OR 2000:py OR 2001:py OR 2002:py OR 2003:py OR 2004:py OR 2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py) AND ('meta analysis'/de OR 'meta analysis topic'/de OR 'systematic review'/de OR 'review'/de))) AND ([adult]/lim OR [aged]/lim)

Table S2 Excluded articles and reasons for exclusion

No.	Article title	Year of publication	Scientific journal or study registry platform	Authors	Study design	Treatment intervention	Reason for exclusion
1	Ketamine and Internalizing Disorders	2019	WHO ICTRP	n/a	n/a	Glutamate-modulating agents	Protocol register
2	Buprenorphine augmentation improved symptoms of OCD, compared to placebo: results from a randomized, double-blind and placebo-controlled clinical trial	2017	Journal of psychiatric research	Ahmadpanah et al.	RCT	Other	Intervention out of scope of the review
3	Buprenorphine augmentation improved symptoms of OCD, compared to placebo: results from a randomized, double-blind and placebo-controlled clinical trial	2017	Journal of psychiatric research	Ahmadpanah et al.	RCT	Other	Duplicate
4	Resistance to antidepressants in OCD patients	2019	Psychotherapy and Psychosomatics	Albert et al.	Review	n/a	Abstract
5	Ondansetron augmentation of serotonin reuptake inhibitors as a treatment strategy in obsessive-compulsive disorder	2015	The Journal of Clinical Psychiatry	Andrade	Review	n/a	Intervention out of scope of the review
6	L-carnosine as an adjuvant to fluvoxamine in treatment of obsessive compulsive disorder: a randomized double-blind study	2017	Human Psychopharmacology: Clinical and Experimental	Arabzadeh et al.	RCT	Other	Duplicate
7	Resistance to antidepressants in OCD patients	2019	WHO ICTRP	n/a	n/a	Other	Protocol register
8	Comparison of drugs, Fluvoxamine and Sertraline in patients with OCD in terms of efficacy and effect on neuro-psychological functions	2020	WHO ICTRP	n/a	n/a	SRI	Protocol register
9	Clinical trials of N-acetylcysteine in psychiatry and neurology: A systematic	2015	Neurosci Biobehav Rev	Deepmala et al.	Systematic review	Glutamate-modulating	Treatment of conditions other

No.	Article title	Year of publication	Scientific journal or study registry platform	Authors	Study design	Treatment intervention agents	Reason for exclusion than OCD
	review						
10	Augmentation of serotonin reuptake inhibitors with antipsychotic drugs in treatment-resistant obsessive-compulsive disorder: A meta-analysis	2017	European Neuropsychopharmacology	Dold et al.	Meta-analysis	Antipsychotics	Poster presentation
11	Comparison of saffron and fluvoxamine in the treatment of mild to moderate obsessive-compulsive disorder: a double blind, randomized clinical trial	2017	Iranian journal of psychiatry	Esalatmanesh et al.	RCT	Other	Intervention out of scope of the review
12	Efficacy of N-acetylcysteine augmentation on obsessive compulsive disorder: a multicenter randomized double blind placebo controlled clinical trial	2017	Iranian journal of psychiatry	Ghanizadeh et al.	RCT	Glutamate-modulating agents	Age
13	Ondansetron or placebo in the augmentation of fluvoxamine response over 8 weeks in obsessive-compulsive disorder	2014	International Clinical Psychopharmacology	Heidari et al.	RCT	Other	Intervention out of scope of the review
14	Plasma oxytocin changes and anti-obsessive response during serotonin reuptake inhibitor treatment: A placebo controlled study	2013	BMC Psychiatry	Humble et al.	RCT	SRI	Primary outcome other than pre- and post-treatment variation of OCD severity, as measured by the reduction of Y-BOCS scores
15	Acute effects of cannabinoids on symptoms of obsessive-compulsive disorder: a human laboratory study	2020	Depression and anxiety	Kayser et al.	RCT	Other	Intervention out of scope of the review
16	Cannabinoid Augmentation of Exposure-Based Psychotherapy for Obsessive-	2020	Journal of clinical psychopharmacology	Kayser et al.	RCT	Other	Intervention out of scope of the

No.	Article title	Year of publication	Scientific journal or study registry platform	Authors	Study design	Treatment intervention	Reason for exclusion
	Compulsive Disorder						review
17	Amantadine as adjuvant therapy in the treatment of moderate to severe obsessive-compulsive disorder: a double-blind randomized trial with placebo control	2019	Psychiatry and clinical neurosciences	Naderi et al.	RCT	Other	Duplicate
18	Randomized Controlled Trial of Intranasal Ketamine vs. Intranasal Midazolam in Individuals With OCD	2014	clinicaltrials.gov	n/a	RCT	Glutamate-modulating agents	Protocol register
19	Acceptance and Commitment Therapy in SSRI-Resistant Obsessive Compulsive Disorder	2016	clinicaltrials.gov	n/a	n/a	Psychotherapy	Intervention out of scope of the review
20	Effects of atorvastatin on treatment-resistant obsessive-compulsive disorder: a double-blind randomized trial	2018	Psychiatria polska	Rahim & Sayyah	RCT	Other	Intervention out of scope of the review
21	Can exposure-based CBT extend the effects of intravenous ketamine in obsessive-compulsive disorder? an open-label trial	2016	J Clin Psychiatry	Rodriguez et al.	Open-label trial	Glutamate-modulating agents	Open-label trial
22	Pilot trial of a brief course of exposure-based CBT in extending IV Ketamines' effects in OCD	2015	Neuropsychopharmacology	Rodriguez et al.		Glutamate-modulating agents	Poster presentation
23	Effect of a novel NMDA receptor modulator, rapastinel (formerly GLYX-13) in OCD: Proof-ofconcept	2016	American Journal of Psychiatry	Rodriguez et al.	Open-label trial	Glutamate-modulating agents	Open-label trial
24	Buprenorphine augmentation improved symptoms of OCD, compared to placebo: Results from a randomized, double-blind and placebo-controlled clinical trial	2017	Pharmacopsychiatry	Sadeghi Bahmani & Ahmadpanah	RCT	Other	Intervention out of scope of the review
25	Effect of selenium as an adjunctive therapy	2018	Archives of Psychiatry and	Sayyah et al.	RCT	Other	Intervention out of

No.	Article title	Year of publication	Scientific journal or study registry platform	Authors	Study design	Treatment intervention	Reason for exclusion
	in patients with treatment-resistant obsessive-compulsive disorder: A pilot randomized double blind placebo-controlled clinical trial		Psychotherapy				scope of the review
26	Ondansetron augmentation for treatment-resistant obsessive-compulsive disorder: a randomized placebo-controlled clinical trial	2019	Iranian red crescent medical journal	Sepehrmanesh et al.	RCT	Other	Intervention out of scope of the review
27	Evaluation of second generation antipsychotics, as augmentative plan, in treatment-resistant obsessive-compulsive disorder	2019	Current psychopharmacology	Shafti & Kaviani	RCT	Antipsychotics	Self-plagiarism
28	Adjunctive quetiapine may help fluvoxamine-resistant obsessive-compulsive disorder among female in-patients: A randomized-controlled study	2019	Psychiatry and Clinical Psychopharmacology	Shafti & Kaviani	RCT	Antipsychotics	Self-plagiarism
29	Celecoxib as an Adjuvant to Fluvoxamine in Moderate to Severe Obsessive-compulsive Disorder: a Double-blind, Placebo-controlled, Randomized Trial	2015	Pharmacopsychiatry	Shalbafan et al.	RCT	Other	Intervention out of scope of the review
30	Fluvoxamine combination therapy with tropisetron for obsessive-compulsive disorder patients: A placebo-controlled, randomized clinical trial	2019	Journal of Psychopharmacology	Shalbafan et al.	RCT	Other	Intervention out of scope of the review
31	Long-term outcome of obsessive-compulsive disorder in adults: a meta-analysis	2014	J Clin Psychiatry	Sharma et al.	Meta-analysis	Other	Individual studies included in this meta-analysis were cohort/prospective studies
32	Clinical utility of repeated intravenous	2020	Asian Journal of Psychiatry	Sharma et al.	Case	Glutamate-	Study design

No.	Article title	Year of publication	Scientific journal or study registry platform	Authors	Study design	Treatment intervention	Reason for exclusion
	ketamine treatment for resistant obsessive-compulsive disorder				series	modulating agents	
33	Randomized controlled trial on the efficacy of panchagavya ghrita in the management of obsessive compulsive disorder	2014	International journal of research in ayurveda and pharmacy	Shihabuddeen et al.	RCT	Other	Intervention out of scope of the review
34	Aripiprazole versus quetiapine in treatment-resistant obsessive-compulsive disorder: a double-blind clinical trial	2015	Therapeutic advances in psychopharmacology	Shafti & Kaviani	RCT	Antipsychotics	Self-plagiarism
35	Double Blind Controlled Study of Adding Folic Acid to Fluoxetine in the Treatment of OCD	2019	Psychiatria Danubina	Tural et al.	RCT	Other	Intervention out of scope of the review
36	Venlafaxine in obsessive-compulsive disorder	1996	Archives of General Psychiatry	Yaryura-Tobias et al.	Letter to the editor	SRI	Primary outcome other than pre- and post-treatment variation of OCD severity, as measured by the reduction of Y-BOCS scores
37	5-Hydroxytryptophan as adjuvant therapy in treatment of moderate to severe obsessive-compulsive disorder: a double-blind randomized trial with placebo control	2020	International clinical psychopharmacology	Yousefzadeh et al.	RCT	Other	Intervention out of scope of the review
38	Combined fluvoxamine and extended-release methylphenidate improved treatment response compared to fluvoxamine alone in patients with treatment-refractory obsessive-compulsive disorder: A randomized double-blind, placebo-controlled study	2019	European Neuropsychopharmacology	Zheng et al.	RCT	Other	Intervention out of scope of the review

Table S3 Systematic review quality assessment with AMSTAR

No.	Title	Year	1st author	Journal	AMSTAR rating
1	Atypical antipsychotic augmentation in SSRI treatment refractory obsessive-compulsive disorder: a systematic review and meta-analysis	2014	Veale	BMC Psychiatry	Moderate
2	Antipsychotic augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: an update meta-analysis of double-blind, randomized, placebo-controlled trials	2015	Dold	Int J Neuropsychopharmacol	Low
3	Second-generation antipsychotics for obsessive compulsive disorder (Review)	2010	Komossa	Cochrane Database Syst Rev	High
4	A systematic review of the use of risperidone, paliperidone and aripiprazole as augmenting agents for obsessive-compulsive disorder	2019	Brakoulias	Expert Opin Pharmacother	Critically Low
5	A systematic review and meta-analysis: Memantine augmentation in moderate to severe obsessive-compulsive disorder	2019	Modarressi	Psychiatry Res	Critically Low
6	Serotonin reuptake inhibitors and memantine for obsessive-compulsive disorder: a meta-analysis of double-blind, randomized, placebo-controlled trials	2018	Kishi	J Alzheimers Dis	Critically Low
7	Early onset of response with selective serotonin reuptake inhibitors in obsessive-compulsive disorder: a meta-analysis	2016	Issari	J Clin Psychiatry	Critically Low
8	Pharmacological and psychotherapeutic interventions for management of obsessive-compulsive disorder in adults: a systematic review and network meta-analysis	2016	Skapinakis	Lancet Psychiatry	Low
9	Meta-analysis of the dose-response relationship of SSRI in obsessive-compulsive disorder	2010	Bloch	Mol Psychiatry	Critically Low
10	Selective serotonin re-uptake inhibitors (SSRIs) versus placebo for obsessive compulsive disorder (OCD)	2008	Soomro	Cochrane Database Syst Rev	High

Table S4 Clinical trial quality assessment with PEDro

No.	Title	Year	First Author	Journal	Total score (max = 11)
1	A comparative, single-blind, randomized study on quetiapine and aripiprazole augmentation in treatment of selective serotonin reuptake inhibitor refractory obsessive-compulsive disorder	2020	Talaei	Can J Physiol Pharmacol	8
2	Comparing escitalopram with sertraline for obsessive and compulsive symptoms in patients with obsessive compulsive disorder: A comparative double blind clinical trial	2018	Mowla	Asian J Psychiatr	9
3	Duloxetine augmentation in resistant obsessive-compulsive disorder: A double-blind controlled clinical trial	2016	Mowla	J Clin Psychopharmacol	10
4	Amantadine as adjuvant therapy in the treatment of moderate to severe obsessive-compulsive disorder: A double-blind randomized trial with placebo control	2019	Naderi	Psychiatry Clin Neurosci	11
5	Efficacy of cognitive behavioural therapy with medication for patients with obsessive-compulsive disorder: A multicentre randomised controlled trial in China	2019	Meng	Journal of Affective Disorders	7
6	Efficacy and tolerability of adjunctive gabapentin and memantine in obsessive compulsive disorder: Double-blind, randomized, placebo-controlled trial	2018	Farnia	J Psychiatr Res	8
7	Randomized Controlled Crossover Trial of Ketamine in Obsessive-Compulsive Disorder: Proof-of-Concept	2013	Rodriguez	Neuropsychopharmacology	8
8	L-carnosine as an adjuvant to fluvoxamine in treatment of obsessive compulsive disorder: A randomized double-blind study	2017	Arabzadeh	Hum Psychopharmacol	11
9	Lamotrigine Augmentation Versus Placebo in Serotonin Reuptake Inhibitors-Resistant Obsessive-Compulsive Disorder: A Randomized Controlled Trial	2016	Khalkhali	Iran J Psychiatry	10
10	Mavoglurant Augmentation in OCD Patients Resistant to Selective Serotonin Reuptake Inhibitors: A Proof-of- Concept, Randomized, Placebo-Controlled, Phase 2 Study	2017	Rutrick	Adv Ther.	10
11	Optimal treatment for obsessive compulsive disorder: A randomized controlled	2018	Fineberg	Int Clin Psychopharmacol	9

No.	Title	Year	First Author	Journal	Total score (max = 11)
	feasibility study of the clinical-effectiveness and cost-effectiveness of cognitive-behavioural therapy, selective serotonin reuptake inhibitors and their combination in the management of obsessive compulsive disorder				
12	N-Acetyl Cysteine (NAC) in the Treatment of Obsessive- Compulsive Disorder: A 16-Week, Double-Blind, Randomised, Placebo-Controlled Study	2015	Sarris	CNS Drugs	8
13	N-acetylcysteine augmentation therapy for moderate-to-severe obsessive–compulsive disorder: randomized, double-blind, placebo-controlled trial	2016	Paydary	J Clin Pharm Ther.	10
14	Randomized, Double-Blind, Placebo-Controlled Trial of N-Acetylcysteine Augmentation for Treatment-Resistant Obsessive-Compulsive Disorder	2017	Costa	J Clin Psychiatry	10
15	N-Acetylcysteine Add-On Treatment in Refractory Obsessive-Compulsive Disorder	2012	Afshar	J Clin Psychopharmacol.	9
16	Six-Month Follow-Up of a Randomized Controlled Trial Augmenting Serotonin Reuptake Inhibitor Treatment With Exposure and Ritual Prevention for Obsessive-Compulsive Disorder	2013	Foa	J Clin Psychiatry	5
17	Pregabalin augmentation for resistant obsessive–compulsive disorder: a double-blind placebo-controlled clinical trial	2020	Mowla	CNS Spectr	8
18	Riluzole augmentation in treatment-refractory obsessive-compulsive disorder: a pilot placebo-controlled trial	2015	Pittenger	J Clin Psychiatry.	10
19	Riluzole in augmentation of fluvoxamine for moderate to severe obsessive–compulsive disorder: Randomized, double-blind, placebo-controlled study	2016	Emamzadehfard	Psychiatry Clin Neurosci.	11
20	Topiramate augmentation in refractory obsessive-compulsive disorder: A randomized, double-blind, placebo-controlled trial	2014	Afshar	J Res Med Sci	10