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Natural Medicines for Psychotic Disorders

A Systematic Review

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Abstract: Patients with psychotic disorders regularly use natural medicines, although it is unclear whether these are effective and safe. The aim of this study was to provide an overview of evidence for improved outcomes by natural medicines. A systematic literature search was performed through Medline, PsycINFO, CINAHL, and Cochrane until May 2015. In 110 randomized controlled trials, evidence was found for glycine, sarcosine, *N*-acetylcysteine, some Chinese and ayurvedic herbs, ginkgo biloba, estradiol, and vitamin B6 to improve psychotic symptoms when added to antipsychotics. Ginkgo biloba and vitamin B6 seemed to reduce tardive dyskinesia and akathisia. Results on other compounds were negative or inconclusive. All natural agents, except reserpine, were well tolerated. Most study samples were small, study periods were generally short, and most results need replication. However, there is some evidence for beneficial effects of certain natural medicines.

Key Words: Psychosis, natural products, complementary medicine

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Despite much progress in treatment options in the last century, the pharmacological treatment of psychotic disorders is often unsatisfactory, as expressed in persistent positive, negative, cognitive and affective symptoms, and problems in social functioning (Kane and Correll, 2010). Psychotic symptoms are often only partially resolved (Rummel-Kluge et al., 2010), especially cognitive and negative symptoms (Buckley and Stahl, 2007). Apart from clozapine, second-generation antipsychotics are generally as effective as first-generation antipsychotics for positive symptoms, but the promise of greater efficacy for negative symptoms has not been fulfilled (Leucht et al., 2012). Many patients continue experiencing persistent symptoms and relapses during treatment with antipsychotics, particularly when they fail to adhere to prescribed medications (Van Os and Kapur, 2009). Psychiatric medication adherence is a problem because many patients do not want them or consider them unnecessary (Cooper et al., 2007), or experience undesired adverse effects (Pai and Vella, 2012). For antipsychotics, these adverse effects include weight gain, sexual dysfunction, glycemic and lipid dysfunction, extrapyramidal symptoms (EPS), and sedation (Stahl, 2008).

Many patients with psychotic disorders use nonconventional medicines or treatments in the hope of decreasing undesired adverse effects or a more successful recovery (Hazra et al., 2010; Stevinson, 2001). Nonconventional medicine includes therapeutic lifestyle changes and complementary and alternative medicine (CAM) (Hoenders, 2013). Complementary medicine comprises diagnostics, treatments, and prevention strategies based on theories accepted in biomedicine and substantiated by some scientific evidence (two or more randomized controlled trials [RCTs]), but for various (cultural or practical) reasons are no part of biomedicine (Hoenders et al., 2011). Alternative medicine comprises diagnostics, treatments, and prevention strategies using other than the basic concepts of biomedicine. So far, there is little proof for the efficacy of the latter treatments and/or considerable controversy about their scientific validation (Lake, 2007). Natural medicine is part of complementary medicine, using agents produced by living organisms (plant, tree, seed, vegetable, fruit, animal, and human) instead of nonnatural (*i.e.*, chemical) agents only being obtained from laboratory experiments (Porter, 1998). Some patients prefer natural medicines, assuming that natural is better and will cause fewer adverse effects. This is obviously not (always) true, as the natural environment contains agents that can be toxic to humans. The molecular structure and dosage of a substance rather than its source determine its effect on human health (Topliss et al., 2002). Besides, herbal medicines can cause undesired effects including interactions with prescription medication (Ernst, 2003a, 2003b).

Hazra et al. (2010) reported a lifetime and 1-year prevalence rate of CAM use in Canadian psychotic outpatients of 88% and 68%, respectively. A major difficulty these patients encounter is the heterogeneity in treatment options with CAM, ranging from possibly interesting agents to useless, or even dangerous, ones (Ernst, 2003b). For instance, the concomitant use of antipsychotics and Chinese herbs was found to induce significantly improved clinical outcomes compared with antipsychotics only (Rathbone et al., 2007). However, a small but significant number of patients concomitantly treated with Chinese herbs have a greater risk of developing worse outcomes (Zhang et al., 2011b).

In recent years, patients' preferences and views have received more attention in making treatment choices (*e.g.*, shared decision making [Elwyn et al., 2000] and "patient-centered care" [Gill, 2013]). The introduction of patient's choice in deciding which antipsychotic to choose has been proposed (Morrison et al., 2012). However, it is difficult for both patients and physicians to make informed decisions in the absence of reliable information on the emerging evidence for CAM or natural medicine. Considering its high usage in psychotic patients, there is an urgent need for readily available scientific information.

This article reviews the literature on the efficacy and safety of natural medicines for psychotic disorders.

REVIEW

Materials and Methods

Literature Search and Study Selection

Studies were identified by a literature search in Medline, PsycINFO, CINAHL, and Cochrane, until May 2015, in accordance

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TABLE 1. Sources of Literature Retrieval and Included Number of Studies

Database	Trials	Reviews	Total
Medline	511	629	1140
CINAHL	62	22	84
PsycINFO	245	129	374
Cochrane	253	20	273
Total	1069	800	1871
Total deduplicated			1467

with the Medline RCT filter. The search terms (MeSH Thesaurus and free search terms) used were schizophrenia, psychosis, psychoses, psychotic (disorder), schizophreniform AND (R)CT, review AND complementary medicines, herbs, vitamins, supplements (search terms, in alphabetical order: alpha lipoic acid [ALA], artemisinin, ascorbic acid, Ayurveda, brahmyadiyoga, branched-chain amino acids [BCAA], Chinese herbs, D-cycloserine, D-serine, daotan decoction, dehydroepiandrosterone [DHEA], docosahexaenoic acid [DHA], eicosapentaenoic acid [EPA], estradiol, fatty acid, fish oil, folic acid, ginkgo biloba, glycine, jiawei lingguizhugan tang, jieyu anshen decoction, L-stepholidine, L-theanine, manganese, methylfolate, *N*-acetylcysteine [NAC], *N*-methylglycine, niacine, omega-3, orengedokuto, rauwolfia serpentina, saikokaryukotsuboreito, sarcosine, sarsasapogenin, selenium, shakuyakukanzoto, shuizhi dahuang mixture, suo quan, tongdatang serial recipe [TDT], traditional Chinese medicine [TCM], vitamin B complex, vitamin B3, vitamin C, vitamin D, vitamin E, and zinc). After systematic deduplication, 1465 hits (abstracts) were retrieved (Table 1).

Next, abstracts about the following topics were included: a) effects of natural medicines on psychotic symptoms in schizophrenia spectrum nonaffective disorders and b) effects of natural medicines on the adverse effects of antipsychotics. Those excluded were a) nonrandomized

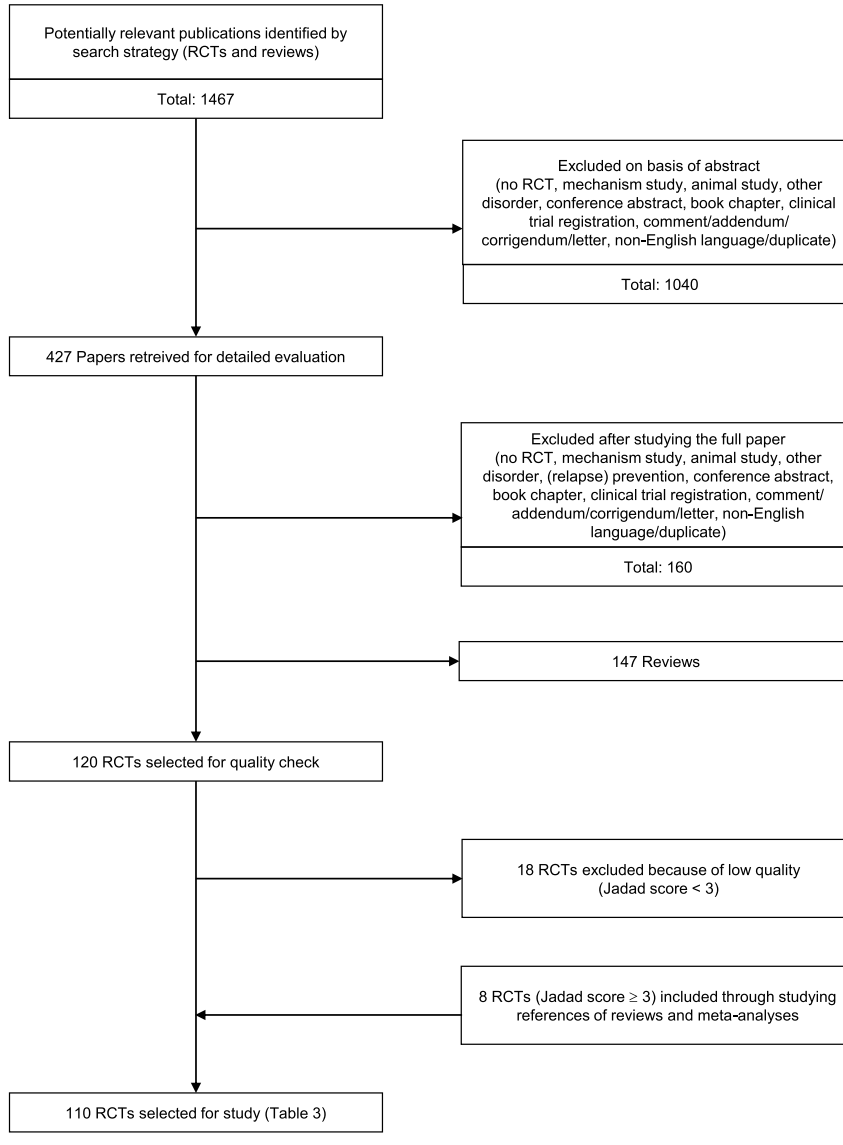

FIGURE 1. Flowchart of study selection.

(controlled) trials; b) mechanism studies exploring the effects of natural medicines; c) animal studies; d) affective disorders/other disorders/no disorder/(relapse) prevention; e) conference abstracts; f) book chapters; g) clinical trial registrations; h) comments, addenda, corrigenda, and letters; i) non-English languages (*e.g.*, Chinese, Japanese, Hebrew, German, and Spanish); and (j) duplicate hits that had not been removed systematically. Second, two authors (H.J.R.H. and A.A.B.V.) independently indicated whether papers—based on the abstracts—should (possibly) be included. Consultation followed about dubious cases and in case of discordance. Thereupon, 427 studies remained, of which the full papers on RCTs were retrieved and studied. Of these, another 160 were excluded. A flowchart of the study selection is presented in Figure 1. We found 147 reviews and checked whether RCTs in their reference lists matching our inclusion criteria were included. Eight RCTs with a Jadad score of 3 or higher (see paragraph on risk of bias assessment and Table 2) found through cross-references were added. Eighteen RCTs were excluded because of a Jadad score less than 3. The reviews (not shown in Table 3) will be contrasted to our findings in the Discussion section.

Classification of Agents

The RCTs included were divided into six groups based on supposed underlying mechanisms of action (Table 3). For a good grasp of the results, we briefly present the working mechanisms of the agents from five groups (not from the group "other substances").

(i) Omega-3 fatty acids. Polyunsaturated fatty acids (PUFAs) are essential for brain functioning (Tsalamanios et al., 2006). They have multiple important biological roles, including membrane functioning, neurotransmission, signal transduction, and eicosanoid synthesis. Research suggests that PUFA level reduction is related to schizophrenia (Berger et al., 2006). Concordant with these findings, omega-3 PUFA may have positive effects in the treatment of schizophrenia (Emsley et al., 2002; Peet, 2008).

(ii) Glutamate. Besides dopamine, glutamate is thought to play a role in schizophrenia (Tsai and Lin, 2010). On the basis of the hypothesis that the glutamatergic system may be compromised in schizophrenia, the use of *N*-methyl-D-aspartate (NMDA) receptor modulators may compensate for alterations in the glutamate system (Singh and Singh, 2011). Agents with coagonistic properties to (glutaminergic) NMDA receptors are glycine (full, endogenous agonist), D-serine (full, endogenous agonist), D-cycloserine (partial, exogenous agonist), D-alanine (partial, endogenous agonist), and sarcosine (= methylglycine, acting as a reuptake inhibitor of glycine and source of glycine). The glycine transporter-1 (GlyT-1) plays a pivotal role in maintaining the glycine concentration within synapses at a subsaturating level. Sarcosine is a GlyT-1 inhibitor, meaning that its presence results in increased glycine concentrations. Lower cerebral glycine levels are suggested to be found in patients with schizophrenia. The administration of sarcosine is therefore proposed to relieve symptoms of schizophrenia when added to nonclozapine antipsychotics (Lane et al., 2006). Whereas the mechanisms of NAC are now beginning to be understood, NAC is probably exerting benefits beyond being a precursor to the antioxidant glutathione, also modulating glutamatergic, neurotropic, and inflammatory pathways (Dean et al., 2011).

(iii) Eastern (Chinese and ayurvedic) herbs. Eastern herbs are provided in the context of treatment with complete systems of medicine that evolved over thousands of years, such as TCM and Ayurveda. These treatments include prescription of herbal compounds, massage, diet, acupuncture, and the regulation of lifestyle (Clifford, 1994; Kaptchuck, 2000). Most clinical studies were performed on acupuncture (beyond the scope of this review) and on herbal compounds.

(iv) B vitamins. Nobel laureate Linus Pauling proposed a way of understanding and treating psychiatric disorders by correcting malfunctions in the body's chemistry, calling this approach "orthomolecular psychiatry" (Pauling, 1968). His idea was partly built on studies by Osmond and Hoffer (1962) and Hoffer and Osmond (1964), reporting good results when treating patients with schizophrenia with large doses of vitamins, especially vitamin B3. Hoffer (1971, 1972) published two more positive results with B vitamins. However, attempts to replicate his findings seem to have failed (Ban and Lehmann, 1975; Wittkopp and Abuzzahab, 1972). The contradicting findings may be explained because vitamine B is suggested to be effective in early psychosis but not in chronic schizophrenia (Hoffer and Osmond, 1964). One of the proposed mechanisms is abnormal one-carbon metabolism due to vitamin deficiencies (Hoffer, 2008). Variable levels of the components of one-carbon metabolism (folic acid [= vitamin B9] and vitamin B12) and consequently altered levels of homocysteine and phospholipid DHA have been reported both in medicated patients and in medication-naive first-episode psychotic patients (Kale et al., 2010). Folate status in patients with schizophrenia correlates inversely with negative symptoms (Goff et al., 2005).

(v) Antioxidants. Oxygen is essential in life but also generates reactive molecules (so-called free radicals) throughout the body. These free radicals are potentially harmful because they can damage essential molecules such as DNA and the enzymes necessary for proper cell functioning. Antioxidants may capture these reactive free radicals and convert them back to less reactive forms of the molecules (Singh

TABLE 2. Jadad Scale for Assessing the Quality of RCTs

Item	Description	Scoring
Randomization	Was the study described as randomized (this includes the use of words such as randomly, random, and randomization)?	**1 point**
	Was the method to generate the sequence of randomization described and appropriate (table of random numbers, computer generated, etc)?	+1 point
	Was the method to generate the sequence of randomization described inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc)?	−1 point
Blinding	Was the study described as double blind?	**1 point**
	Was the method of double blinding described and was it appropriate (identical placebo, active placebo, dummy, etc)?	+1 point
	Was the study described as double blind but the method of blinding was inappropriate (*e.g.*, comparison of tablet *vs* injection with no double dummy)?	−1 point
An account of all patients	Was there a description of withdrawals and dropouts?	**1 point**

TABLE 3. Overview of Effects of Natural Medicines for Psychotic Disorders

Study[a]	Study Population	Dosage of Natural Medication (Daily)	Also AP?	AP Dosage	Effects of Natural Medicines[b]						Adverse Effects of Natural Medicines[b]	*N*, Design, Description of Treatment/ Control Group	Dropout	Duration of Study (and Follow-Up, If Applicable)	Jadad Score
					Negative sx	Positive sx	Cognitive sx	Depressive sx	General Psychopathology	Adverse Side-Effects AP					
1. Omega-3															
Vaddadi et al. (1989)	Patients predominantly diagnosed with schizophrenia (mean age 52.7 y) with movement disorders	12 capsules containing 45 mg γ-linolenic acid + 360 mg linoleic acid	Yes				+ (WMS)		+ (CPRS)	+ EPS (SAS) 0 TD (AIMS)	0	*N* = 48; c-o (21 AP + efamol/plac, 17 AP + plac/efamol)	10 (ns per gr)	2× 16 wk	4
Fenton et al. (2001)	Outpatients (18–65 y) with schizophrenia or schizoaffective disorder	3 g ethyl EPA	Yes		0 (PANSS)	0 (PANSS)	0 (RBANS)	0 (MADRS)	0 (CGI)	0 TD (AIMS), EPS (SAS)	Respiratory infection and diarrhea	*N* = 90 (45 AP + EPA, 45 AP + plac)	15 (8 in EPA gr, 7 in plac gr)	16 wk	4
Peet et al. (2001)[c]	Outpatients (mean age 44.2 y) with schizophrenia	2 g EPA or 2 g DHA	Yes		0 (PANSS)	+ (PANSS)					n.r.	*N* = 55 (45 ct; 15 AP + EPA, 16 AP + DHA, 14 AP + plac)	10; ns per gr	3 mo	4
Peet et al. (2001)[c]	Outpatients (mean age 44.2 y) with schizophrenia	2 g EPA or 2 g DHA	At start no, later in trial yes			+ (PANSS)			+ (less use of antipsychotic medication)		0	*N* = 30 (15 EPA, 15 plac)	3 in plac gr, 1 in EPA gr	3 mo	4
Emsley et al. (2002)	Patients (18–55 y) with schizophrenia	3 g E-EPA	Yes		0 (PANSS)	0 (PANSS)			+ (PANSS subscale)	0 EPS (ESRS) + dyskinesia (ESRS)	0	*N* = 40 (20 AP + E-EPA, 20 AP + plac)	1 in E-EPA gr	12 wk	3
Peet and Horrobin (2002)	Outpatients (20–62 y) with schizophrenia	1, 2, or 4 g E-EPA	Yes		0 (PANSS) + (PANSS for 2g gr on Cloz)	0 (PANSS) + (PANSS for 2g gr on Cloz)		0 (MADRS)	0 (PANSS) + (PANSS for 2g gr on Cloz)	0 EPS (SAS, LUNSERS), akathisia (BARS), TD (AIMS)	0	*N* = 122 (31 AP + plac, 29 AP + 1 gr E-E, 28 AP + 2 gr E-E, 27 AP + 4 gr E-E)	1 in plac gr, 5 in 1g gr, 5 in 2g gr, 2 in 4g gr	12 wk	4
Emsley et al. (2006, 2008)[d]	Patients (18–60 y) with schizophrenia or schizoaffective disorder meeting *DSM-IV* criteria for TD	2 g E-EPA	Yes		0 (PANSS)	0 (PANSS)				0 dyskinesia, EPS (ESRS) 0 HDL, LDL, triglycerides, serum prolactin, Hb, blood pressure, heart rate	Increase in bleeding time and BMI	*N* = 84 (42 AP + E-EPA, 42 AP + plac)	11 in E-EPA gr, 18 in plac gr	12 wk	4
Berger et al. (2007) (15–29 year olds)	Patients (15–29 y) with at least 1 current psychotic symptom	2 g E-EPA	Risp, Olan, or Quet		0 (SANS)				0 (BPRS, CGI, GAF, SOFAS)	+ EPS (SAS), less use of AP	0	*N* = 80 (40 AP + E-EPA, 40 AP + plac)	5 in E-EPA gr, 6 in plac gr	12 wk	5
Manteghiy et al. (2008)	Inpatients diagnosed with schizophrenia (mean age 37.4 y)	6 g fish oil + 1080 mg EPA + 720 mg DHA	Risp		0 (PANSS)	0 (PANSS)		0 (PANSS)	0 (PANSS)		Gastrointestinal adverse effects (in 3)	*N* = 106, 85 c-t (42 Risp + ω-3, 43 Risp + plac)	21, ns per gr	6 wk	4
Toktam et al. (2010)	Patients diagnosed with schizophrenia, bipolar I disorder, or schizoaffective disorder (18–60 y)	900 mg EPA/DHA	Olan						0 (FBS, fasting insulin, HbA_{1c}, HOMA-IR)		n.r.	*N* = 41 (20 Olan + ω-3 [4 schizophr/ schizoaff], 21 Olan + plac [8 schizophr/ schizoaff])	n.r.	6 wk	3
Omega-3 + vits E and C															
Bentsen et al. (2013) (omega-3 and vits E + C)	Patients with schizophrenia or related psychoses (18–39 y)	2 g EPA and/or 364 mg vit E + 1 g vit C	Yes		0 (PANNS, in high PUFA patients)	0 (PANNS in high PUFA patients) − (PANNS, EPA and vits alone, in low PUFA patients) 0 (PANNS, EPA + vits, in low PUFA patients)			− (more use of AP in vits gr)		SAEs in 9 patients (no link between treatment and number of SAEs)	*N* = 104 (25 AP + plac + plac, 28 AP + plac + vit E + C, 33 AP + EPA + plac, 18 AP + EPA + vit E + C)	3 in plac + plac gr, 8 in plac + vit gr, 7 in EPA + plac gr, 6 in EPA + vit gr	16 wk	4

2. Glutamate														
Glycine														
Javitt et al. (1994)	Male patients diagnosed with schizophrenia (mean age 37 y)	2–0.4 g/kg body weight	Yes		+ (PANSS)	0 (PANSS)			0 (PANSS subscale)	0 EPS (ESRS), TD (AIMS)	No SAEs; temporarily lower extremity weakness (1)	*N* = 14 (7 AP + glyc, 7 AP + plac)	0	8 wk d-b, 8 wk glyc for everyone	4
Heresco et al. (1996)	Inpatients (22–60 y) diagnosed with schizophrenia, considered to be treatment resistant	4–0.8 g/kg body weight	Yes		+ (PANSS)	0 (PANSS)	+ (PANSS subscale)	+ (PANSS subscale)	+ (PANSS subscale)	0 TD (AIMS), EPS (SAS)	0	*N* = 12 c-o (7 AP + glyc/plac, 4 AP + plac/glyc)	1 (on plac, in plac/glyc gr)	2× 6 wk, 2 wk wo before and in between	4
Heresco-Levy et al. (1999)	Patients (mean age 38.8 y) diagnosed with schizophrenia who are treatment resistant	4–0.8 g/kg body weight	Yes		+ (PANSS)	0 (PANSS)	+ (PANSS subscale)	+ (PANSS subscale)	+ (BPRS)	0 TD (AIMS), EPS (SAS)	Nausea and vomiting (1)	*N* = 22 c-o (10 AP + plac/glyc, 9 AP + glyc/plac)	3 (2 on plac, 1 on glyc)	2× 6 wk, 2 wk wo before and in between	4
Potkin et al. (1999)	Hospitalized patients (age n.r.) with chronic schizophrenia	30 g	Cloz	400–1200 mg/day	0 (SANS)	− (BPRS subscale)			0 (BPRS)		0	*N* = 24 (12 Cloz + glyc, 12 Cloz + plac)	3 in glyc gr, 2 in plac gr	12 wk	4
Evins et al. (2000)	Clinically stable outpatients (mean age 39 y) with schizophrenia	60 g	Cloz		0 (SANS, PANSS)	0 (PANSS)	0 (PANSS subscale)		0 (BPRS)		n.r.	*N* = 30 (27 ct; 14 Cloz + glyc, 13 Cloz + plac)	2 on plac, 1 on glyc	8 wk	4
Javitt et al. (2001)	Inpatients (mean age 39.6 y) diagnosed with schizophrenia	0.8 g/kg body weight	Yes		+ (PANSS)		+ (PANSS subscale)	+ (PANSS subscale)		0 EPS (SAS), akathisia (BARS), TD (AIMS)	0	*N* = 12 c-o (6 AP + glyc/plac, 6 AP + plac/glyc)	0	2× 6 wk, 4 wk wo before and 2 wk in between	4
Heresco et al. (2004)	Inpatients (22–60 y) diagnosed with schizophrenia, who are treatment resistant, and presently treated	0.8 g/kg body weight	Olan, Risp		+ (PANSS)	+ (PANSS)	+ (PANSS subscale)	+ (PANSS subscale)	+ (BPRS)	+ EPS (SAS), TD (AIMS)	No SAEs; mild upper gastrointestinal tract discomfort with nausea (2)	*N* = 17 c-o (1 gr AP + glyc/plac, 1 gr AP + plac/glyc)	3 on glyc	2× 6 wk, 2 wk wo before and in between	4
Diaz et al. (2005)	Inpatients (mean age 44.7 y) diagnosed with schizophrenia, who are treatment resistant, and presently treated	60 g	Yes		0 (PANSS)	0 (PANSS)			0 (BPRS, GAF)	0 EPS (ESRS, SAS)	nausea and vomiting (1)	*N* = 12 c-o (6 AP + plac/glyc, 6 AP + glyc/plac)	1 on glyc	28 wk	3
Buchanan et al. (2007) (also reported under D-cycloserine)	Patients (18–64 y) diagnosed with schizophrenia or schizoaffective disorder	n.r.	Yes, no Cloz		+ (SANS) for glyc by conventional antipsychotics		0 (neuropsychological test battery)		0 (BPRS, CGI)	0 EPS (SAS), TD (AIMS)	nausea and dry mouth	*N* = 165 (55 AP + both plac, 56 AP + d-c + plac, 54 AP + glyc + plac)	10 in plac gr, 10 in d-c gr, 12 in glyc gr	16 wk	3
D-Serine															
Tsai et al. (1998)	Day program and inpatients patients (mean age 33 y) diagnosed with schizophrenia	30 mg/kg body weight	Yes		+ (SANS)	+ (PANSS)	+ (PANSS subscale, WCST)	0 (HAM-D)	+ (CGI) 0 (PANSS subscale)	0 TD (AIMS), akathisia (BARS), EPS (SAS)	no SAEs; insomnia (2), nausea (2), diarrhea (1), constipation (1)	*N* = 31 (17 AP + plac, 14 AP + d-s)	3 in plac gr, 0 in d-s gr	6 wk	4
Tsai et al. (1999)	Inpatients (mean age 41 y) diagnosed with schizophrenia	30 mg/kg body weight	Cloz		0 (PANSS, SANS)	0 (PANSS)	0 (PANSS subscale, WCST)	0 (HAM-D)	0 (PANSS subscale, CGI)	0 TD (AIMS), akathisia (BARS), EPS (SAS)	0	*N* = 20 (10 Cloz + d-s, 10 Cloz + plac)	n.r.	6 wk	3
Heresco-Levy et al. (2005)	Inpatients (18–70 y) diagnosed with schizophrenia, treatment resistant, and presently treated	30 mg/kg body weight	Olan, Risp		+ (PANSS, SANS)	+ (PANSS)	+ (PANSS subscale)	+ (PANSS subscale)	+ (BPRS)	+ EPS (SAS), TD (AIMS)	0	*N* = 39, c-o (19 AP + d-s/plac, 20 AP + plac/d-s)	3	2× 6 wk, 2 wk wo before and 3 wk wo in between	4
Lane et al. (2005) (also reported under sarcosine)	Inpatients (18–60 y) diagnosed with schizophrenia	2 g or 2 g sarcosine	Risp	6 mg/day or less	0 (SANS)	0 (PANSS)	0 (PANSS subscale)	0 (PANSS subscale)	0 (PANSS subscale)	0 EPS (SAS), akathisia (BARS), TD (AIMS)	no SAEs; *e.g.*, weight gain, palpitations, insomnia, fatigability, orthostatic dizziness, weight loss, tension, salivation	*N* = 65 (23 Risp + plac, 21 Risp + d-s, 21 Risp + sar)	3 in plac gr, 2 in d-s gr, 3 in sar gr	6 wk	5
Lane et al. (2010) (also reported under sarcosine)	Inpatients (18–60 y) diagnosed with schizophrenia	2 g or 2 g sarcosine	Yes		0 (PANSS, SANS)	0 (PANSS)	0 (PANSS subscale)	0 (PANSS subscale)	0 (QoL, GAF)	0 EPS (SAS), akathisia (BARS), TD (AIMS)	no SAEs; *e.g.*, weight gain, insomnia, fatigability, sedation, palpitations	*N* = 60 (20 AP + plac, 20 AP + sar, 20 AP + d-s)	1 in sar gr, 4 in d-s gr, 4 in plac gr	6 wk	5

(Continued on next page)

TABLE 3. *(Continued)*

Study[a]	Study Population	Dosage of Natural Medication (Daily)	Also AP?	AP Dosage	Effects of Natural Medicines[b]						Adverse Effects of Natural Medicines[b]	*N*, Design, Description of Treatment/ Control Group	Dropout	Duration of Study (and Follow-Up, If Applicable)	Jadad Score
					Negative sx	Positive sx	Cognitive sx	Depressive sx	General Psychopathology	Adverse Side-Effects AP					
Weiser et al. (2012)	Inpatients and outpatients (18–64 y) diagnosed with schizophrenia or schizoaffective disorder	2 g	Yes		0 (SANS, PANSS)	0 (PANSS)	0 (MATRICS)		0 (PANSS subscale)		Mouth sores	*N* = 195 (97 AP + d-s, 98 AP + plac)	23 in d-s gr, 23 in plac gr	16 wk	5
D'Souza et al. (2013) (D-serine + computerized cognitive retraining [CRT])	Patients (18–65 y) diagnosed with schizophrenia or schizoaffective disorder	30 mg/kg body weight	Yes, not Lam, Car or Cloz		0 (PANSS)	0 (PANNS)	0 (CGI) + (differential site effects on individual test performance for d-s + CRT)	0 (CDS)	0 (PANNS subscale)	0 EPS (NRS) + Akathisia (BARS, in Indian d-s gr)		*N* = 104 (27 d-s + control CRT [1], 27 plac + CRT [2], 24 d-s + CRT [3], 24 plac + control CRT [4])	2 (11 at fu) in gr 1, 5 (10 at fu) in gr 2, 3 (9 at fu) gr 3, 3 (9 at fu) in gr 4	12 wk + 24 wk fu	4
Ermilov et al. (2013)	Inpatients (mean age 50 y) diagnosed with schizophrenia	3 g	Olan in AP gr	15–30 mg	+ (PANNS, less improvement in d-s gr than in Ola gr)	+ (PANNS, less improvement in d-s gr than in Ola gr)				0 EPS (SAS), TD (AIMS)	0	*N* = 18 (10 d-s, 8 Olan)	5 in d-s gr, 3 in Olan gr	10 wk	4
D-Cycloserine															
Rosse et al. (1996)	Patients (mean age 38.1 y) with chronic schizophrenia	30 mg	Mol	50 mg t.i.d.	0 (SANS)	0 (BPRS)			0 (BPRS)		n.r.	*N* = 13 (3 Mol + 10 mg d-c, 6 Mol + 30 mg d-c, 4 Mol + plac)	0	4 wk	3
Van Berckel (1999)	Patients (18–60 y) diagnosed with schizophrenia	100 mg	yes		0 (PANSS)	− (PANSS)			− (PANNS subscale, CGI)	0 EPS (ESRS)	0	*N* = 26 (13 AP + d-c, 13 AP + plac)	1 in d-c gr	8 wk	4
Heresco-Levy et al. (2002)	Patients (mean age 40.0 y) diagnosed with schizophrenia, who were treatment resistant	50 mg	Yes		+ (PANSS)	0 (PANSS)		0 (HAM-D)	+ (PANSS subscale)	0 EPS (SAS), TD (AIMS)	0	*N* = 24, c-o (16 ct, 8 AP + d-c/plac, 8 AP + plac/d-c)	3 on d-c, 5 on plac	2× 6 wk, 2 wk wo in between	3
Duncan et al. (2004)	Male subjects (mean age 51.8 y) diagnosed with schizophrenia, who displayed prominent negative symptoms	50 mg	Yes		0 (SANS, BPRS subscale)		0 (CPT, SSTMSP)		0 (BPRS)	0 EPS (SAS)	0	*N* = 22 (10 AP + d-c, 12 AP + plac)	0	4 wk	4
Goff et al. (2005)[c]	Outpatients (mean age 46.5 y) diagnosed with schizophrenia	50 mg	Yes		0 (PANSS, SANS)	0 (PANSS)	0 (*e.g.*, WAIS scales, Stroop, WCST)	0 (HAM-D)	0 (GAS, QoL)	0 EPS (SAS), TD (AIMS)	n.r.	*N* = 55 (27 AP + d-c, 28 AP + plac)	13 in d-c gr, 16 in plac gr)	24 wk	4
Yurgelun-Todd et al. (2005)	Inpatients and outpatients (36–58 y) diagnosed with schizophrenia	50 mg	Yes		+ (PANSS)	0 (PANSS)	+ (temporal lobe activation) 0 (frontal lobe activation)				n.r.	*N* = 12 (6 AP + d-c, 6 AP + plac)	0	8 wk	4
Buchanan et al. (2007) (also reported under glycine)	Patients (18–64 y) diagnosed with schizophrenia or schizoaffective disorder	n.r.	Yes, no Cloz		0 (SANS)		0 (neuro-psychological test battery)		0 (BPRS, CGI)	0 EPS (SAS), TD (AIMS)	0	*N* = 165 (55 AP + plac + plac, 56 AP + d-c + plac, 54 AP + glyc + plac)	10 in plac gr, 10 in d-c gr, 12 in glyc gr	16 wk	3
Goff et al. (2008)	Stable patients (18–65 y) diagnosed with schizophrenia	50 mg	Yes, no Cloz		+ (SANS)	0 (PANSS)	0 (cognitive test battery)		0 (CGI)		0	*N* = 38 (19 AP + d-c, 19 AP + plac)	3 in d-c gr, 2 (3 at f.u.) in plac gr	8 wk, f.u. + 2 wk	5
Gottlieb et al. (2011)	Outpatients (18–65 y) diagnosed with schizophrenia or schizoaffective disorder (depressed type), and who had experienced persistent delusions despite treatment with AP	50 mg	Yes			0 (SAPS, PSYRATS) + (first d-c, greater reductions in delusional severity)	0 (ABA, PRT-BT) + (first d-c, greater reductions in belief conviction)				0	*N* = 21, c-o (11 AP + d-c/plac, 10 AP + plac/d-c)	1 in plac – d-c gr	3 wk, 3 visits, 2 doses (visit 1 and 2)	4
Cain et al. (2014)	Outpatients (18–65 y) diagnosed with schizophrenia or schizoaffective disorder, depressed type	50 mg	Yes, no Cloz		0 (SANS) + (SANS for subs with clinically sig nx at baseline)		0 (MATRICS) + (auditory discrimination task)				0	*N* = 40 (36 were treated; 18 AP + d-c, 18 AP + plac)	4 b-t; 1 in d-c gr, 3 in plac gr	8 wk	4

D-Alanine															
Tsai et al. (2006)	Day program and inpatients (mean age 33 y) diagnosed with schizophrenia	100 mg/kg body weight	Yes		+ (SANS)	+ (PANSS)	+ (PANSS subscale)	0 (HAM-D)	+ (CGI) 0 (PANSS subscale)	0 TD (AIMS), akathisia (BARS), EPS (SAS)	no SAEs; insomnia and nausea (1)	*N* = 32 (18 AP + plac, 14 AP + d-a)	1 in plac gr	6 wk	4
Sarcosine															
Tsai et al. (2004)	Day program and inpatients (mean age 32 y) diagnosed with schizophrenia	2 g	Yes		+ (SANS)	+ (PANSS)	+ (PANSS subscale)	0 (HAM-D)	+ (PANSS subscale, BPRS)	0 EPS (SAS), akathisia (BARS), TD (AIMS)	no SAEs; tachycardia (2)	*N* = 38 (17 AP + sar, 21 AP + plac)	2 (1 in each gr)	6 wk	4
Lane et al. (2005) (also reported under D-serine)	Inpatients (18–60 y) diagnosed with schizophrenia	2 g or 2 g D-serine	Risp	6 mg/day or less	+ (SANS)	+ (PANSS)	+ (PANSS subscale)	+ (PANSS subscale)	+ (PANSS subscale)	0 EPS (SAS), akathisia (BARS), TD (AIMS)	no SAEs; *e.g.*, weight gain, palpitations, insomnia, fatigability, orthostatic dizziness, weight loss, tension, salivation	*N* = 65 (23 Risp + plac, 21 Risp + d-s, 21 Risp + sar)	3 in plac gr, 2 in d-s gr, 3 in sar gr	6 wk	5
Lane et al. (2006)	Inpatients (mean age 36 y) diagnosed with schizophrenia	2 g	Cloz		0 (PANSS)	0 (PANSS)	0 (PANSS subscale)	0 (PANSS subscale)	0 (PANSS subscale)	0 EPS (SAS), akathisia (BARS), TD (AIMS)	insomnia (2)	*N* = 20 (10 Cloz + sar, 10 Cloz + plac)	0	6 wk	4
Lane et al. (2008)	Hospitalized patients (18–60 y) diagnosed with schizophrenia	1 or 2 g	no		0 (PANSS)	0 (PANSS)			0 (QoL)		No SAEs; insomnia (6), weight gain (3), sedation (1), constipation (1), fatigability (1)	*N* = 20 (11 2g sar, 9 1g sar)	3 in 1g gr, 1 in 2g gr	6 wk	4
Lane et al. (2010) (also reported under D-serine)	Inpatients (18–60 y) diagnosed with schizophrenia	2 or 2 g D-serine	Yes		+ (PANSS, SANS)	+ (PANSS)	+ (PANSS subscale)	+ (PANSS subscale)	+ (QoL, GAF)	0 EPS (SAS), akathisia (BARS), TD (AIMS)	No SAEs; *e.g.*, weight gain, insomnia, fatigability, sedation, palpitations	*N* = 60 (20 AP + plac, 20 AP + sar, 20 AP + d-s)	1 in sar gr, 4 on d-s, 4 in plac gr	6 wk	5
N-acetyl cysteine															
Berk et al. (2008)	Inpatients and outpatients (mean age 36.6 y) diagnosed with schizophrenia	2 g	Yes		+ (PANNS)	0 (PANSS)	0 (digit span, word learning, trail making, verbal fluency)		+ (CGI) 0 (GAF, SOFAS)	0 TD (AIMS), EPS (SAS) + akathisia (BARS)	0	*N* = 140 (71 AP + plac, 69 AP + NAC)	56, ns per gr	24 wk, f.u. at 28 wk	4
Lavoie et al. (2008)	Outpatients (mean age 31.9 y) diagnosed with schizophrenia	2 g	Yes				0 (auditory discrimination task, P300) + (MMN)				n.r.	*N* = 9 c-o (2 d-o; 5 AP + NAC/plac, 2 AP + plac/NAC)	2, ns per gr	2× 2 wk	3
3. Eastern herbs															
Naidoo (1956)	Inpatients (17–70 y) with schizophrenia	10 mg Reserpine	no						+ (clinical improvement)		No SAEs; nasal congestion, periorbital edema, diarrhea, epigastric pain, salivating, pseudo-parkinsonian state, severe headaches, deep pains in limbs	*N* = 80 (20 plac [A], 20 serpasil [B], 20 plac + ect [C], 20 serpasil + ect [D])	n.r.	11 wk of plac or treatment, then treatment for all groups (A + B serpasil, C + D reserpine) ns for how many weeks	3
Mahal et al. (1976)	Outpatients (16–45 y) with schizophrenia	12 g Tagara or 12 g Brahmyadiyoga	Chlor only in AP-gr	First month 200 mg, second month 300 mg	+/0 (B better than plac and Tagara, no sign dif with chlor)	+/0 (B better than plac and Tagara, no sign dif with chlor)			0 (MPQ, SAE)		n.r.	*N* = 136 (108 ct; 27 tagara, 27 B, 27 plac, 27 Chlor)	28 (ns per gr)	2 mo	3
Mundewadi et al. (2008) (am: Bacopa monnieri, nardostachys jatamansi)	Patients (18–60 y) with schizophrenia	800 mg Bacopa Monnieri (active) plus 400 mg Nardostachys Jatamansi (active)	Olan in control gr	10 mg dd	+ (as effective as AP) (PANSS)	+ (as effective as AP) (PANSS)			+ (as effective as AP) (clinical improvement)	+ (less weight gain than AP)	No SAEs; vomiting and diarrhea (2)	*N* = 200 (97 ayurvedic medicine, 103 AP)	12 in am gr, 15 in AP gr	78 wk	3
Chen et al. (2008a, 2009)[d]	Patients (18–45 y) diagnosed with schizophrenia	2.7 g WSKY	Risp	Max 8 mg/day	0 (SANS, PANSS)	0 (PANSS)	+ (WCST)	+ (HAM-D)	+ (QoL, SDSS, lower use of AP)	0 TD (AIMS, RSESE)	No SAEs; *e.g.*, tremor, insomnia, akathisia, somnolence, headache, weight gain, constipation	*N* = 120 (60 risp + WSKY, 60 risp + plac)	2 in WSKY gr, 2 in plac gr	8 wk	5

(Continued on next page)

TABLE 3. *(Continued)*

Study[a]	Study Population	Dosage of Natural Medication (Daily)	Also AP?	AP Dosage	Effects of Natural Medicines[b]						Adverse Effects of Natural Medicines[b]	*N*, Design, Description of Treatment/ Control Group	Dropout	Duration of Study (and Follow-Up, If Applicable)	Jadad Score
					Negative sx	Positive sx	Cognitive sx	Depressive sx	General Psychopathology	Adverse Side-Effects AP					
Chen et al. (2008b)	Inpatients and outpatients (18–45 y) diagnosed with schizophrenia	2.7 g WSKY	Risp		0 (PANSS)	0 (PANSS)	0 (WCST)	0 (HAM-D)	+ (SDSS)	0 TD (AIMS, RSESE)	No SAEs; *e.g.*, tremor, akathisia, insomnia, somnolence, constipation, weight gain, sight dim	*N* = 200 (100 risp + WSKY, 100 risp + plac)	2 in plac gr, 4 in WKSY gr	8 wk	4
Xiao et al. (2011)	Patients (mean age 50.5 y) diagnosed with schizophrenia	200 mg Sarsasapogenin	Risp		0 (PANSS)	0 (PANSS)	0 (WMS, mWAIS)		0 (CGI)		No SAEs; *e.g.*, abnormal ECG, tremor, akathisia, drowsiness	*N* = 90 (44 risp + plac, 46 risp + sars)	5 in plac gr, 5 in sars gr	8 wk	5
4. B vits															
Vit B1 (thiamin)															
Sacks et al. (1989) (also acetazolamide)	Patients (mean age 39.1 y) with schizophrenia	2 g Acetazolamide plus 1.5 g Thiamine	Yes		+ (SAPS)	+ (SANS)					No SAEs; some increased urination	*N* = 26, c-o (24 ct; 13 AP + A + T/plac, 11AP + plac/A + T	2, ns per gr	2× 8 wk, 4 wk wo before and in between	4
Vit B3 (niacin/nicotinic acid, niacinamide/nicotinamide)															
Kline et al. (1967) (nicotinamide)	Male inpatients (23–52 y) with schizophrenia	1 g	Yes 5 of 20				0 Free drawing test		0 BPRS; 0 RRS; 0 WPRS		n.r.	*N* = 20 (10 plac, 10 1g or 2g NAD)	0	20 days	5
Meltzer et al. (1969) (nicotinamide)	Male patients (20–35 y) with schizophrenia	2 g	Thiorida-zine in 5 of 10						0 IMPS 0 BDI		n.r.	*N* = 10 c-o (5 plac + plac/NAD/plac, 5 thi + plac/NAD/plac)	1	9 wk	3
Greenbaum (1970) (niacinamide) (4–12 year olds)	Children (4–12 y) diagnosed with schizophrenia	n.r.	n.r.				0 (WISC, SFBT)		0 (behaviour ratings)			*N* = 57 (17 niac, 16 niac + tranquilizer, 24 plac)	0	6 mo	3
Ramsay et al. (1970) (nicotinic acid, nicotinamide)	Patients (mean age 29.5 yr) diagnosed with schizophrenia	Nicotinic acid 3 g or nicotinamide 3 g	Pheno-thiazide						0 BPRS 0 MMPI 0 HOD			*N* = 30 (Ph + 10 nic, Ph + 10 na, 10 Ph + plac)	0	6 mo	4
Ananth et al. (1972) (nicotinic acid, nicotinamide)	Inpatients (mean age 26.6 y) with schizophrenia	Nicotinic acid 2 g or nicotinamide 2 g	Chlor						+ (BPRS, less chlor in nic gr) − (more chlor in na gr, more hospital days in nic gr and na gr)		No SAEs; rash in nic gr (1) and in na gr (1)	*N* = 30 (9 chlor + nic, 10 chlor + na, 11 chlor + plac)	6 ct, 3 in na gr, 2 in plac gr, 1 in nic gr	2 y	4
McGrath et al. (1972) (nicotinamide)	Inpatients (mean age 31.9 yr) diagnosed with schizophrenia	3 g	Yes						0 (recovery rate)		n.r.	*N* = 184 (132 na, 133 plac)	43 in na gr, 38 in plac gr	12 mo	4
Ananth et al. (1973) (nicotinic acid) (also reported under vit B6)	Inpatients (mean age 41.7 y) with schizophrenia	3 g	Yes						+ (BPRS, NOSIE)		Abnormal liver function, leukopenia, weight loss, in nic gr (5,1,1), in nic + pyr gr (5,1,2), weight gain (1), hypotension (2) in nic + pyr gr	*N* = 30 (10 nic + pyr, 10 nic + plac, 10 plac + pyr)	1 in pyr gr, 2 in nic + pyr gr, 1 in nic gr	48 wk	4
Wittenborn et al. (1973) (niacin)	Inpatients and outpatients (mean age 28.8 y) with schizophrenia	3 g	Yes						0 (hospitalization, use of tranquilizers, WPRS, RNRS)		Pigmented hyperkeratosis (in about 1/3rd of the subjects)	*N* = 140 (75 ct, 47 3000 mg niacin, 28 6 mg niacin)	65 ns per gr	24 mo	3
Deutsch et al. (1977) (nicotinic acid, nicotinamide)	Inpatients (age n.r.) with schizophrenia	3150 mg Nicotinic acid or 3150 mg nicotinamide	Yes						0 (BPRS, CGI, NOSIEI)		14 different adverse effects, not mentioned	*N* = 30 (10 AP + nic, 10 AP + na, 10 AP + plac)	1 in nm gr, 5 in nic gr	48 wk	4
Petrie et al. (1981) (nicotinic acid) (also reported under vit B6)	Inpatients (mean age 41.7 yr) with schizophrenia	300 mg	Yes						+ (BPRS, nic gr and pyr gr) 0 (BPRS, nic + pyr gr) 0 (NOSIE)		Abnormal liver function tests, hypotension, weight loss, flushing of the skin, dermatitis	*N* = 30 10 AP + nic + pyr, 10 AP + nic + plac, 10 AP + pyr + plac)	1 in pyr gr, 2 in nic + pyr gr, 1 in nic gr	48 wk	4

Vit B6 (pyridoxine)														
Ananth et al. (1973) (also reported under vit B3)	Inpatients (mean age 26.6 yr) with schizophrenia	75 mg	Yes						+ (BPRS, NOSIE)		Nausea and vomiting (1), dizziness (1), tachycardia (1), weight gain (1), flushing of skin (2), dermatitis (2)	*N* = 30 (10 nic + pyr, 10 nic + plac, 10 plac + pyr)	1 in pyr gr, 2 in nic + pyr gr, 1 in nic gr	48 wk	4
Petrie et al. (1981) (also reported under vit B3)	Inpatients (mean age 41.7 y) with schizophrenia	75 mg	Yes						+ (BPRS, nic gr and pyr gr) 0 (BPRS, nic + pyr gr)		Abnormal liver function tests, hypotension, weight loss, flushing of the skin, dermatitis	*N* = 30 (10 AP + nic + pyr, 10 AP + nic + plac, 10 AP + pyr + plac)	1 in pyr gr, 2 in nic + pyr gr, 1 in nic gr	48 wk	4
Lerner et al. (2001, 2002)[d]	Inpatients (28–71 y) with schizophrenia or schizoaffective disorder	400 mg	Yes		0 (PANSS)	0 (PANSS)			0 (CGI)	+ TD (ESRS)	0	*N* = 15, c-o (8 AP + vit B6/plac, 7 AP + plac/vit B6)	0	2× 4 wk, 1 wk wo in between	3
Lerner et al. (2004)	Inpatients (mean age 42.4 y) with schizophrenia or schizoaffective disorder	1200 mg	Yes						+ (CGI, BPRS)	+ NIA (BARS)	0	*N* = 20 (10 AP + vit B6, 10 AP + plac)	0	5 days	4
Miodownik et al. (2006) (also a group on mianserin)	Inpatients (mean age 41.8 y) with schizophrenia, schizoaffective disorder or bipolar affective disorder	1200 mg	Yes						+ (BPRS, CGI; in B6 gr and mian gr)	+ NIA (BARS)	0	*N* = 60 (23 AP + vit B6, 20 AP + mian, 17 AP + plac)	0	5 days	4
Lerner et al. (2007)	Inpatients (mean age 46.8 y) diagnosed with schizophrenia or schizoaffective disorder	1200 mg	Yes							+ TD (ESRS)	No SAEs; acne (1), allergic reaction (1)	*N* = 50, c-o (28 AP + vit B6/plac, 22 AP + plac/vit B6)	10 on vit B6, 4 on plac	26 wk (2×12 wk + 2 wk wo in between)	3
Vit B9 (folic acid)															
Godfrey et al. (1990) (methylfolate)	Outpatients (mean age 44.8 y) diagnosed with major depression or schizophrenia	15 mg	Yes						+ (clinical rating scale)		n.r.	*N* = 17 (subgr of 41; 9 AP + met, 8 AP + plac)	0	6 mo	3
Hill et al. (2011) (folic acid)	Outpatients (18–68 y) diagnosed with schizophrenia	2 mg	Yes		0 (SANS) + effect of MTHFR gt)	0 (PANSS)	0 (*e.g.*, WAIS, WCST)	0 (CDSS)	0 (GAF, QoL)		n.r.	*N* = 38 (19 AP + fa, 19 AP + plac)	5 in B11 gr, 5 in plac gr	12 wk	4
Vits B1, B6, and B12															
Joshi (1982)	Patients (age n.r.) with acute schizophrenic psychosis	100 mg B1 plus 50 mg B6 plus 1000 µg B12	Chlor, Trif	150 mg dd, 15 mg dd					0 (behavior scale) + less ect's in vit gr		0	*N* = 60 (30 vit inj, 30 plac inj)	1 ns per gr	4 wk, f-u 1 yr	4
Vits B6, B9, and B12															
Levine et al. (2006)	Inpatients (age n.r.) with schizophrenia	2 mg folic acid plus 25 mg pyridoxine plus 400 µg B12	Yes		+ (PANSS)	+ (PANSS)	+ (WCST) 0 (DS, RAVLT, CFD)			0 TD (AIMS)	n.r.	*N* = 55, c-o (20 AP + vit/plac, 22 AP + plac/vit)	13 (2 ns; 5 on plac, 6 on vits)	2× 3 mo	3
Vits B9 and B12															
Roffman et al. (2013) (folic acid and B12)	Outpatients (mean age 45.5 y) with schizophrenia	2 mg folate plus 400 µg B12	Yes		+ (SANS, no sig dif, mostly for FOLH1 genotypes)	+ (PANSS, no sig dif)					Worsening of psychosis in 3 (2 in vit gr, 1 in plac gr)	*N* = 140 (94 AP + fa + B12, 46 AP + plac)	16 in fol + B12 gr, 3 in plac gr	16 wk	4
5. Antioxidants															
Vit C															
Bhavani et al. (1962)	Male inpatients (20–30 y) with schizophrenia	10 mg/kg body weight	No				0 (*e.g.*, recall, attention, imitation)		0 (motor functioning)		n.r.	*N* = 31 (15 ascorbic acid, 16 plac)	n.r.	10 days	4
Dakhale et al. (2005)	Outpatients (mean age 38.6 y) diagnosed with schizophrenia	500 mg	Olan, Quet, Zipr	10/200/40 mg/day					+ (BPRS)	+ (reduce of serum MDA)	0	*N* = 40 (20 AP + vit C, 20 AP + plac)	4 in plac gr, 1 in vit gr	8 wk	5
Ginkgo biloba															
Zhou et al. (1999)	Patients (mean age 43.4 y) with schizophrenia	360 mg	Hal	0,25 mg kg^{-1} day^{-1}	0 (SANS)	+ (SAPS)			+ (SOD levels)	+ (less behavioural toxicity and symptoms of nervous system)	0	*N* = 54 (27 Hal + EGb, 27 Hal + plac)	n.r.	12 wk	3

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TABLE 3. *(Continued)*

Study[a]	Study Population	Dosage of Natural Medication (Daily)	Also AP?	AP Dosage	Effects of Natural Medicines[b]						Adverse Effects of Natural Medicines[b]	N, Design, Description of Treatment/ Control Group	Dropout	Duration of Study (and Follow-Up, If Applicable)	Jadad Score
					Negative sx	Positive sx	Cognitive sx	Depressive sx	General Psychopathology	Adverse Side-Effects AP					
Zhang et al. (2011a),	Patients (mean age 44.4 y) diagnosed with schizophrenia	360 mg	Hal	0,25 mg kg^{-1} day^{-1}	0 (SANS)	+ (SAPS)			+ (SOD levels)	+ (less behavioural toxicity and symptoms of nervous system)	n.r.	N = 82 (43 Hal + Egb, 39 Hal + plac)	n.r.	12 wk	3
Zhang et al. (2001b, 2006)[d]	Inpatients (mean age 44.6 y) diagnosed with schizophrenia	360 mg	Hal	0,25 mg kg^{-1} day^{-1}	0 (SANS)	+ (SAPS)			0 (BPRS)	+ (better immune function, less behavioural toxicity and symptoms of nervous system)	0	N = 109 (56 Hal + Egb, 53 Hal + plac)	1 in Egb gr, 5 in plac gr	12 wk	4
Zhang et al. (2011a)	Male inpatients (mean age 45.3 y) diagnosed with schizophrenia	240 mg	Yes		0 (PANSS)	0 (PANSS)	0 (CPT, Stroop)			+ TD (AIMS)	0	N = 157 (78 AP + Egb, 79 AP + plac)	4 in plac gr, 1 in Egb gr	12 wk, f.u. +6 mnts	5
Vit E															
Elkashef et al. (1990)	Outpatients (mean age 56.6 y) diagnosed with schizophrenia or schizoaffective disorder	1200 IU	Yes						0 (BPRS)	+ EPS (AIMS)	no SAEs; mild diarrhea (1)	N = 10, c-o (8 ct; 5 AP + vit E/plac, 3 AP + plac/vit E)	2, ns per gr	2× 4 wk, 2 wk wo before	3
Schmidt et al. (1991)	Inpatients and outpatients (mean age 45 y) with schizophrenia, depression, or schizoaffective psychoses	200 IU	Yes							0 EPA (AIMS)	Negligible	N = 19, c-o (11 AP + vit E/plac, 8 AP + plac/vit E)	2 in each gr	2× 14 days	3
Egan et al. (1992)	Inpatients and one outpatient (mean age 43.9 y) diagnosed with schizophrenia, schizotypal personality, bipolar disorder, or depression	1600 IU	Yes							+ TD (AIMS) for those <5 y	0	N = 21, c-o (10 AP + vit E/plac, 11 AP + plac/vit E)	1, ns per gr	2× 6 wk	3
Shriqui et al. (1992)	Patients (18–70 y) with TD	1200 IU	Yes							0 EPS (AIMS, ESRS)	n.r.	N = 27, c-o (1 gr AP + vit E/plac, 1 gr AP + plac/vit E)	0	2× 6 wk, 2–3 wk wo in between	3
Adler et al. (1993)	Inpatients and outpatients (age n.r.) with TD	1600 IU	Yes							+ TD (AIMS)	0	N = 29 (28 ct; 16 AP + vit E, 12 AP + plac)	3; 1 ns per gr; 2 on vit E	8–12 wk	4
Akhtar et al. (1993)	Inpatients (mean age 54.8 y) with TD	1200 IU	Yes							+ TD (TDRS)	0	N = 32 (17 AP + vit E, 15 AP + plac)	0	4 wk	4
Dabiri et al. (1994)	Outpatients (30–70 y) with TD	1200 IU	Yes							+ TD (AIMS)	Diarrhea (in 1)	N = 12 (6 AP + vit E, 6 AP + plac)	1 in vit E gr	12 wk	3
Lam et al. (1994)	Inpatients (mean age 61.8 y) diagnosed with schizophrenia	1200 IU	Yes						0 (BPRS)	0 TD (AIMS)	n.r.	N = 16, c-o (1 gr AP + vit E/plac, 1 gr AP + plac/vit E)	4, ns per gr	2× 6 wk, 2 wk wo before and in between	3
Lohr and Caligiuri (1996)	Patients (mean age 48,8 y) with schizophrenia, bipolar disorder, or unipolar disorder	1600 IU	Yes						0 (BPRS)	+ TD (AIMS)	n.r.	N = 55 (35 ct, 17 AP + vit e, 18 AP + plac)	20, ns per gr	2 mo	4
Dorevitch et al. (1997a)	Patients (mean age 64.6 y) diagnosed with schizophrenia or schizoaffective disorder	1600 IU	Yes						0 (BPRS)	0 TD (AIMS)	0	N = 40, c-o (1 gr AP + plac/vit E, 1 gr AP + vit E/plac)	2 on plac	2× 8 wk, 4 wk wo in between	3
Dorevitch et al. (1997b)	Patients (mean age 63.2 y) diagnosed with schizophrenia	1600 IU	Yes							0 TD (AIMS, CPK levels)	n.r.	N = 10, c-o (1 gr AP + vit E/plac, 1 gr AP + plac/vit E)	n.r.	2× 8 wk, 4 wk wo in between	3
Adler et al. (1999)	Patients (mean age 50.4 y) diagnosed with schizophrenia or schizoaffective disorder	1600 IU	Flu, Hal, Risp						0 (BPRS, GAF)	0 TD (AIMS), akathisia (BARS), EPS (SAS)	0	N = 158 (73 AP + vit E, 85 AP + plac)	22 in vit E gr, 29 in plac gr	1 y	5

Salmasi et al. (2009)	Patients (18–49 y) with schizophrenia	1200 IU	Olan						0 (insulin resistance)	n.r.	*N* = 36 (32 ct, 15 Olan + vit E, 17 Olan + plac)	4, ns per gr	8 wk	3
Melatonin														
Shamir et al. (2001)	Inpatients (mean age 64.2 y) diagnosed with schizophrenia	10 mg	Yes						+ TD (AIMS)	0	*N* = 24, c-o (22 ct, 10 AP + plac/mel, 12 AP + mel/plac)	2, ns per gr	2× 6 wk, 4 wk wo in between	4
6. Other substances														
Multivitamins														
Altman et al. (1973)	Inpatients (mean age 72 y) with schizophrenia or organic brain syndrome	15 mg B1 plus 10 mg B2 plus 5 mg B6 plus 50 mg niacinamideplus 10 mg calcium pantothenate plus 300 mg vit C	Yes						0 (MIBS)	0	*N* = 151 (75 AP + vit, 76 AP + plac) of which 81 with schizophrenia	6 in vit gr, 13 in plac gr	6 wk	4
Vaughan and McConaghy (1999)	Outpatients (mean age 31 y) diagnosed with schizophrenia	6000 IU vit A plus 1345 mg B1 plus 3520 mg B3 plus 6223 mg B6 plus 25 mg B12 plus 2822 mg vit C plus 204 mg vit E plus 5.2 mg folic acid	Yes						0 (BSI, BDI)	0	*N* = 22 (10 AP + vit E + diet treatment, 9 AP + plac + diet challenge)	1 in plac gr, 0 in vit E gr	5 mo	4
Hormones														
Prange (1979) (protilerin)	Female inpatients (mean age 32.7 y) diagnosed with schizophrenia	0.5 mg protilerin or 2 mg niacin, both once intravenous	No						+ (BPRS)	0	*N* = 12, c-o (6 Pro/niac, 6 niac/Pro)	0	2× 15 days	4
Akhondzadeh et al. (2003) (estradiol)	Patients (mean age 28.0 y) diagnosed with schizophrenia	0.5 mg	Hal	0 (PANSS)	+ (PANSS)			+ (PANSS subscale)		n.r.	*N* = 32 (16 Hal + estr, 16 Hal + plac)	0	8 wk	3
Strous et al. (2003) (DHEA)	Inpatients (mean age 37.4 y) diagnosed with schizophrenia	100 mg	Yes	+ (PANSS, SANS)	0 (PANSS)		+ (HAM-D)	+ (PANSS sub scale) + (HAM-A)		n.r.	*N* = 30 (15 AP + DHEA, 15 AP + plac)	3 in plac gr	6 wk	4
Nachshoni et al. (2005) (DHEA)	Inpatients (mean age 40.8 y) diagnosed with schizophrenia or schizoaffective disorder	100 mg	Yes					0 (BPRS)	+ pakinsonism (SHRS)	0	*N* = 34 (18 AP + DHEA, 16 AP + plac)	3 in DHEA gr, 1 in plac gr	7 days	4
Ritsner et al. (2006) (DHEA)	Patients (mean age 36.4 y) diagnosed with schizophrenia or schizoaffective disorder	200 mg	Yes	+ (PANNS)	+ (PANNS)	+ (subscales of the CANTAB)	+ (PANNS subscale)	0 (QoL)	0 TD (AIMS), EPS (ESRS)	0	*N* = 62, c-o (1 gr AP + DHEA/plac, 1 gr AP + plac/DHEA)	7 ns per gr	2× 6 wk	4
Strous et al. (2007) (DHEA)	Inpatients (mean age 34.0 y) diagnosed with schizophrenia	150 mg	Olan	0 (SANS)		0 (neutcognitive battery)			+ akathisia (BARS), EPS (SAS)		*N* = 40 (20 Olan + DHEA, 20 Olan + plac)	4 in DHEA gr, 5 in plac gr	Olan	
Ko et al. (2008) (testosterone)	Male inpatients (mean age 36.7 y) diagnosed with schizophrenia	5 mg	Yes	+ (PANNS)	0 (PANNS)		0 (CDSS)		0 (DIEPSS)	0	*N* = 30 (15 AP + plac, 15 AP + tes)	2 in tes gr, 2 in plac gr; +5 in tes gr at f-u, + 4 in plac gr at f-u	1× 4 wk, 2 wk f-u	4
Kulkarni et al. (2008) (estradiol)	Female inpatients and outpatients (mean age 33.6 y) diagnosed with schizophrenia, schizoaffective disorder, or schizophreniform disorder	100 µg	Yes	0 (PANSS)	+ (PANSS)	+ (PANSS)		+ (PANSS subscale)		n.r.	*N* = 102 (56 AP + estr, 46 AP + plac)	5 estr gr, 10 plac gr	28 days	5
Ritsner (2010) (DHEA and PREG)	Outpatients (mean age 35.8 y) diagnosed with schizophrenia or schizoaffective disorder	30 or 200 mg PREG or 400 mg DHEA	Yes	0 for all groups (PANSS)	+ for 30 mg/ PREG gr 0 for 200 mg PREG/400 mg DHEA gr (PANSS)	0 for all groups (CANTAB)		0 for all groups (CGI, GAF)	+ for 30 mg PREG/400 mg DHEA gr 0 for 200 mg PREG gr on EPS (ESRS) 0 for all groups on akathisia (BARS)	0	*N* = 58 (16 AP + PREG 30 mg, 10 AP + PREG 200 mg, 16 AP + DHEA 400 mg, 16 AP + plac)	2 in 30 mg PREG gr, 4 in 200 mg PREG gr, 3 in 400 mg DHEA gr, 5 in plac gr	8 wk	5

(Continued on next page)

TABLE 3. *(Continued)*

Study[a]	Study Population	Dosage of Natural Medication (Daily)	Also AP?	AP Dosage	Effects of Natural Medicines[b]						Adverse Effects of Natural Medicines[b]	*N*, Design, Description of Treatment/ Control Group	Dropout	Duration of Study (and Follow-Up, If Applicable)	Jadad Score
					Negative sx	Positive sx	Cognitive sx	Depressive sx	General Psychopathology	Adverse Side-Effects AP					
Kulkarni et al. (2011) (estradiol)	Male patients (mean age 32.0 y) diagnosed with schizophrenia, schizoaffective disorder, or schizophreniform disorder	2 mg	Yes		0 (PANSS)	0 (PANSS)			+ (PANSS subscale)		0	*N* = 53 (26 AP + estr, 27 AP + plac)	0	14 days	3
Inositol															
Levine et al. (1994)	Inpatients (mean age 41.5 y) diagnosed with schizophrenia	12 g	Yes		0 (PANNS)	0 (PANNS)					n.r.	*N* = 14, c-o (12 ct ; 7 AP + inositol/plac, 5 AP + plac/inositol)	2, ns per gr	2× 4 wk, no wo	3
Gamma-hydroxybutyrate															
Schulz et al. (1981)	Patients (mean age 25 y) diagnosed with schizophrenia	16 g	n.r.						0 (BPRS)		0	*N* = 7 (all patients plac/GHB/plac)	0	10–29 days	3
Levy et al. (1983)	Male inpatients (mean age 43.6 y) diagnosed with schizophrenia	12 g	Flu	5 mg/d					0 (BPRS, CGI)		no SAEs; asymptomatic bradycardia in 1	*N* = 11, c-o (1 gr Flu + GHB/chl hy, 1 gr Flu + chl hy/GHB)	1 on plac	2× 3 wk	3
Des-tyr-gamma-endorphin															
Verhoeven et al. (1979)	Patients (mean age 38.3 y) with chronic schizophrenic schizoaffective psychosis	1 mg	Yes			+ (psychotic symptoms rating scale)			+ (contact, emotional responsiveness)		0	*N* = 6, c-o (3 AP + DTGe/plac, 3 AP + plac/DTGe)	0	2× 8 days, 6 wk f-u	4
Artemisinin															
Dickerson et al. (2011)	Outpatients (mean age 47.3 y) diagnosed with schizophrenia or schizoaffective disorder	200 mg	Yes		–	–			–		0	*N* = 66 (33 AP + art., 33 AP)	9 (7 in art. gr, 3 in AP gr)	12 wk	4
Wang et al. (2014)	Inpatients and outpatients (mean age 23.9 y) diagnosed with schizophrenia or schizophreniform disorder	80 mg artemether	Ris	1–6 mg	+	–	–		–		0	*N* = 100 (50 AP + artemether, 50 AP)	12 (4 in artemether gr, 4 in AP gr)	8 wk	4

N.B. When "Also AP?" is answered with "yes," then the subjects used different types of AP; when 1 AP is mentioned, then all used that one.

Vitamin B3 can be administered in the form of niacin, nicotinic acid, niacinamide, or nicotinamide.

NMDA agonists: full, endogenous: glycine, D-serine; partial: D-cycloserine (exogenous), D-alanine (endogenous).

Glycine transporter inhibitor (GlyT-1): sarcosine, also called *N*-methylglycine.

Vitamin B9 can be administered in the form of folic acid and methylfolate.

A, acetazolamide; ABA, Alternative Beliefs Assessment; AIMS, Abnormal Involuntary Movement Scale; α-LA, alpha-lipoid acid; am, ayurvedic medicine; AP, antipsychotics; B, brahmyadiyoga; BARS, Barnes Akathisia Rating Scale; BDI, Behaviour Disturbance Inventory; BMI, body mass index; BPD, borderline personality disorder; BPRS, Brief Psychiatric Rating Scale; BSI, Brief Symptom Inventory; b-t, before treatment; CANTAB, Cambridge Automated Neuropsychological Test Battery; Car, carbamazepine; CDSS, Calgary Depression Scale for Schizophrenia; CFD, Complex Figure Drawing; CGI, clinical global impression scale; chl hy, chloral hydrate; Chlor, chlorpromazine; chol, cholesterol; Cloz, clozapine; c-o, cross-over; CPK, serum creatine phosphokinase; CPRS, Comprehensive Psychopathological Rating Scale; CPT, Continuous Performance Test; ct, completed treatment; d-a, D-alanine; d-c, D-cycloserine; d-b, double-blind; dd, daily dose; DIEPSS, Drug-Induced Extrapyramidal Symptoms Scale; d-o, dropout; DS, digit span; d-s, D-serine; DTGe, des-tyr-gamma-endorphin; ECG, electrocardiogram; ECT, electroconvulsive therapy; E-E, ethyl-eicosapoentaeonate; E-EPA, ethyl-eicosapentaenoic acid; Egb, extract of gingko biloba; ESRS, Extrapyramidal Rating Scale; estr, estradiol; fa, folic acid; FBS, fasting blood sugar; Flu, Fluphenazine; Fol, folate; FOLH1, folate hydrolase 1; f-u, follow-up; GAF, Global Assessment of Functioning; GAS, galactorrhea amenorrhea syndrome; glyc, glycerine; gr, group; Hal, Haloperidol; HAM-A, Hamilton Anxiety Scale; HAM-D, Hamilton Depression Scale; Hb, hemoglobin; HbA1c, hemoglobin A1c; HDL, high-density lipoproteine; HOD, Hoffer-Osmond Diagnostic; HOMA-IR, homeostatic model assessment of insulin resistance; IMPS, inpatient multidimensional psychiatric scale; inj, injection; IU, international unit; Lam, lamotrigine; LDL, low-density lipoproteine; LUNSERS, Liverpool University Neuroleptic Side Effects Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MATRICS, Measurement and Treatment Research to Improve Cognition in Schizophrenia; MDA, malondiadehyde; mel, melatonine; met, methylfolate; mian, mianserin; MIBS, inpatient behaviour form; MMN, mismatch negativity; MMPI, Minnesota Multiphasic Personality Inventory; Mol, molindone; MPQ, multiphasic questionnaire; MTHFR gt, methylenetetrahydrofolate reductase genotype; mWAIS, Modified Chinese version of the Wechsler Adult Intelligence Scale; na, nicotinamide; NAD, nicotinamide adenine dinucleotide; niac, niacinamide; nic, nicotinic acid; NOSIE, Nurses Observation Scale for Inpatient Evaluation; n.r., not reported; NRS, Simpson-Angus Neurological Rating Scale; ns, not specified; nx, negative symptoms; Olan, olanzapine; ω-3, omega-3; PANSS, Positive and Negative Syndrom Scale; Ph, phenothiazide; plac, placebo; POET, Perception of Emotions Test; Pro, protirelin; PRT-BT, Probability Reasoning Task–Bead Task; PSYRATS, Psychotic Symptom Rating Scales; pyr, pyridoxine; Quet, quetiapine; QoL, quality of life; RAVLT, Rey Auditory Verbal Learning Test; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; Ris, risperidone; RNRS, Rutgers Nurse's Rating Scale; RRS, Rockland Rating Scale; RSESE, Rating Scale for Extrapyramidal Side Effects; SAE, spiral after effect; SAEs, serious adverse events; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; sar, sarcosine; saus, sarsasapogenin; SAS, Simpson-Angus Scale; schizoaff, schizoaffective; schizophr, schizophrenia; SDSS, social disability screening schedule; SFBT, Sequin Form Biard Test; SHRS, St. Hans Rating Scale; sig (dif), significant (difference); SOD, superoxide dismutase; SOFAS, Social and Occupational Functioning Assessment Scale; SOPS, Scale of Psychosis-risk Symptoms; SSTMSP, Sternberg Short Term Memory Scanning Paradigm; subs, subjects; sx, symptoms; T, thiamine; TDRS, Tardive Dyskenesia Rating Scale; tes, testosterone; thi, thioridazine; t.i.d., three times a day; Trif, Trifluperazine; vit(s), vitamin(s); WAIS, Wechsler Adult Intelligence Scale; WCST, Wisconsin Card Sorting Test; WISC, Wechsler Intelligense Scale for Children; wk, week(s); WMS, Wechsler Memory Scale; wo, washout; WPRS, Wittenborn Psychiatric Rating Scale; WSKY, Warm-Supplementing Kidney Yang; y, year(s); Zipr, Ziprasidone.

[a]Classified per agent, in order of year of publication.

[b]Scoring of effects: + = positive effect, − = negative effect, 0 = no effect.

[c]Two separate trials published in one article.

[d]One trial, published in two articles.

[e]Papers not identified in original search but found in reference lists or otherwise.

et al., 2010). Research suggests that oxidative damage (maybe due to defective enzyme systems) may contribute to the course and outcome of schizophrenia (Fendri et al., 2006; Mahadik and Mukherjee, 1996; Mahadik et al., 2001) and is already present in patients with first-episode psychosis (Flatow et al., 2013).

Ascorbic acid (vitamin C), an antioxidant vitamin, plays an important role in protecting free radical-induced damage in the body. It is present in brain tissue and dopamine-dominant areas in higher concentrations compared with other organs (Harrison and May, 2009). Ginkgo biloba, an extract of the leaves of the ginkgo biloba tree, is also suggested to have antioxidant properties (Maclennan et al., 2002), improving brain circulation at the microvascular level (Kuboto et al., 2001; Sun et al., 2003; Yan et al., 2008) and, thus, improving outcome in psychosis.

Long-term treatment with antipsychotics is associated with a variety of movement disorders, including tardive dyskinesia (TD). Both dopamine receptor supersensitivity and oxidative stress-induced neurotoxicity in the nigrostriatal system are suggested to be involved in its pathogenesis (Kulkarni and Naidu, 2003). The pineal hormone melatonin is a potent antioxidant and attenuates dopaminergic activity in the striatum and dopamine release from the hypothalamus (Shamir et al., 2001). Thus, treatment with antioxidative agents may have a beneficial effect for both treatment of psychotic symptoms and prevention of TD. Vitamin E has been suggested for TD because it is a lipid-soluble antioxidant that decreases free radical formation (Herrera and Barbas, 2001).

Risk of Bias Assessment

Two assessors (A.A.B.V. and N.K.V.) independently rated the methodological quality of the eligible RCTs using the Jadad scale (Jadad et al., 1996). Interrater agreement on the Jadad scores before consensus discussion amounted to 0.83. Besides, H.J.R.H. independently rated a random selection of 17 papers (15%) from the selected RCTs. Interrater agreement of all three assessors was 0.71. Any scoring disagreements between the assessors were resolved through consensus discussion between these three authors. The 110 RCTs with a Jadad score of 3 or higher were included in the current review, categorized into six groups (see the Classification of agents section).

For each of the 110 studies fulfilling the selection criteria, the following assessments were made: which natural agent was used; was this combined with antipsychotics, and if so, which antipsychotics and what dosage; the effect of the natural agent on negative, positive, cognitive, depressive, and general symptoms and on adverse effects of antipsychotics; possible adverse effects of the natural agent; number of participants in the study; control group characteristics; number of dropouts; study duration; and Jadad score. The results are shown in Table 3.

Results

In total, 110 RCTs that matched the inclusion criteria were identified. Detailed effects are given in Table 3. Most of the studies were performed in the United States, followed by (in decreasing order) Israel, Canada, Taiwan, China, India, United Kingdom, Australia, Iran, South Africa, Switzerland, the Netherlands, Austria, Ireland, Korea, and Norway.

(i) Omega-3 Fatty Acids

Eleven RCTs on omega-3 were included (Bentsen et al., 2013; Berger et al., 2007; Emsley et al., 2002, 2006, 2008; Fenton et al., 2001; Manteghiy et al., 2008; Peet et al., 2001; Peet and Horrobin, 2002; Toktam et al., 2010; Vaddadi et al., 1989), and one combined omega-3 with vitamins E and C (Bentsen et al., 2013). In studies combining antipsychotics with omega-3 PUFA, one (from five) study on negative symptoms in schizophrenia found some positive effect (in patients using clozapine; Peet and Horrobin, 2002), two (from four) found some positive effect on positive symptoms (Peet et al., 2001; Peet and Horrobin, 2002; one only in patients using clozapine [Peet and Horrobin, 2002]), one (from two) on cognitive symptoms (Vaddadi et al., 1989), none (from three) on depressive symptoms, and four (from eight) on general psychopathology (Emsley et al., 2002; Peet et al., 2001; Peet and Horrobin, 2002; Vaddadi et al., 1989; one only in patients using clozapine [Peet and Horrobin, 2002]). One (from one) study on omega-3 PUFA without antipsychotics reported a decrease of positive symptoms (Peet et al., 2001). Three (from six) reported less adverse effects of antipsychotics (EPS and/or dyskinesia) (Berger et al., 2007; Emsley et al., 2002; Vaddadi et al., 1989). Two studies reported less use of antipsychotics in the omega-3 PUFA group (Berger et al., 2007; Peet et al., 2001). One study reported an increase in positive symptoms by omega-3 (EPA), but only among those with low levels of red blood cell PUFA. This effect disappeared when EPA was combined with vitamin E and vitamin C (Bentsen et al., 2013). Some nonsevere adverse effects of omega-3 PUFA were reported, such as mild gastrointestinal problems and increased bleeding time.

(ii) Glutamate

Nine RCTs on glycine (Buchanan et al., 2007; Diaz et al., 2005; Evins et al., 2000; Heresco et al., 1996, 2004; Heresco-Levy et al., 1999; Javitt et al., 1994, 2001; Potkin et al., 1999), eight on D-serine (D'Souza et al., 2013; Ermilov et al., 2013; Heresco-Levy et al., 2005; Lane et al., 2005, 2010; Tsai et al., 1998, 1999; Weiser et al., 2012), ten on D-cycloserine (Buchanan et al., 2007; Cain et al., 2014; Duncan et al., 2004; Goff et al., 2005, 2008; Gottlieb et al., 2011; Heresco-Levy et al., 2002; Rosse et al., 1996; Van Berckel et al., 1999; Yurgelun-Todd et al., 2005), one on D-alanine (Tsai et al., 2006), five on sarcosine (Lane et al., 2005, 2006, 2008, 2010; Tsai et al., 2004), and two on NAC (Berk et al., 2008; Lavoie et al., 2008) were included.

Glycine improved negative symptoms when combined with antipsychotics in six (from seven) studies (Buchanan et al., 2007; Heresco et al., 1996, 2004; Heresco-Levy et al., 1999; Javitt et al., 1994, 2001), but not when combined with clozapine (two studies) (Potkin et al., 1999; Evins et al., 2000). Positive symptoms improved in one study (Heresco et al., 2004), worsened in another (with clozapine) (Potkin et al., 1999), and did not change in five (from seven) studies (Diaz et al., 2005; Evins et al., 2000; Heresco et al., 1996; Heresco-Levy et al., 1999; Javitt et al., 1994); cognitive improvement was shown in four (Heresco et al., 1996, 2004; Heresco-Levy et al., 1999; Heresco et al., 2004; Javitt et al., 2001) and no change in two (from seven) studies (Buchanan et al., 2007; Evins et al., 2000); depressive symptoms diminished in four (from four) studies (Heresco et al., 1996, 2004; Heresco-Levy et al., 1999; Javitt et al., 2001); and improvement of general psychopathology was shown in three (from eight) studies (Heresco et al., 1996, 2004; Heresco-Levy et al., 1999). No adverse effects of glycine were reported, except some mild gastrointestinal complaints.

D-Serine was shown to improve positive, negative, and cognitive symptoms and general psychopathology in two (from six) studies when added to antipsychotics (Heresco-Levy et al., 2005; Tsai et al., 1998). The three largest studies with the highest Jadad score did not show a significant effect of D-serine on any symptom (Lane et al., 2005; Lane et al., 2010; Weiser et al., 2012). In four (from six) studies, D-serine did not improve adverse effects of antipsychotics (Lane et al., 2005, 2010; Tsai et al., 1998, 1999). Insomnia, weight gain, palpitations, and other adverse effects of D-serine were reported. One study found improvement by D-serine without antipsychotics, but this was significantly less compared with the improvement in the olanzapine group; D-serine, however, caused less adverse effects (Ermilov et al., 2013).

D-Cycloserine showed an improvement of negative symptoms in three (from nine) studies when added to antipsychotics (Goff et al., 2008; Heresco-Levy et al., 2002; Yurgelun-Todd et al., 2005); some

improvement of positive symptoms in one (Gottlieb et al., 2011) and worsening in another study (from seven) (Van Berckel et al., 1999); and little or no effect on cognitive and depressive symptoms or general psychopathology and no improvement of adverse effects of antipsychotics was shown. Five (from five) studies found no improvement of adverse effects of antipsychotics (Buchanan et al., 2007; Duncan et al., 2004; Goff et al., 2005; Heresco-Levy et al., 2002; Van Berckel et al., 1999). No studies were reported on D-cycloserine without antipsychotics. No adverse effects of D-cycloserine were reported.

The only study on D-alanine reported positive effects when added to antipsychotics on negative, positive, cognitive, and general symptoms, but no effect on depressive symptoms (Tsai et al., 2006). No effect on adverse effects of antipsychotics was found. Adverse effects of D-alanine (insomnia and nausea) were reported.

All three studies combining sarcosine with antipsychotics (not clozapine) found positive effects in almost all symptom domains (Lane et al., 2005, 2010; Tsai et al., 2004). When combined with clozapine (one study), no treatment effects were found (Lane et al., 2006). In addition, when given without antipsychotics (one study), sarcosine did not improve symptoms (Lane et al., 2008). Sarcosine did not improve adverse effects of antipsychotics in four (from four) studies (Lane et al., 2005, 2006, 2010; Tsai et al., 2004). Adverse effects of sarcosine included weight gain, insomnia, palpitations, dizziness, and sedation.

One large study on NAC added to antipsychotics reported improved positive symptoms but no improvement of negative, cognitive, or general symptoms and no improvement of adverse effects of antipsychotics (Berk et al., 2008), whereas one small study found some improvement of cognitive symptoms (Lavoie et al., 2008). The large study (Berk et al., 2008) reported that there were no adverse effects, and in the small study (Lavoie et al., 2008), occurrence of any adverse effect was not mentioned.

(iii) Eastern (Chinese and Ayurvedic) Herbs

Many studies on Eastern herbs were found, but only six had a Jadad score of three or higher (Chen et al., 2008a, 2008b, 2009; Mahal et al., 1976; Mundewadi et al., 2008; Naidoo, 1956). One old study on reserpine found "clinical improvement" after 11 weeks compared with placebo in 80 patients not treated with antipsychotics but with electroconvulsice therapy (Naidoo, 1956). Several adverse effects were reported: nasal congestion, periorbital edema, diarrhea, epigastric pain, salivating, pseudo-Parkinsonian state, severe headaches, and deep pains in limbs. Another old study (Mahal et al., 1976) found positive effects of brahmyadiyoga without antipsychotics compared with placebo and equal to chlorpromazin in 136 patients with schizophrenia (Mahal et al., 1976); no adverse effects were reported. Four (from six) more recent studies found significant effects on general psychopathology when adding ayurvedic herbs (reserpine: one study [Naidoo, 1956]; bacopa monnieri and nardostachys jatamansi: one study [Mundewadi et al., 2008]; a mixture of 13 Chinese herbs: two studies [Chen et al., 2008a, 2008b, 2009]) to antipsychotics.

The ayurvedic herbs were compared with 10 mg of olanzapine in a 76-week noninferiority study in 200 patients. No statistically significant differences were found between both groups examining improvement of positive and negative symptoms and general psychopathology. The ayurvedic group had less weight gain (Mundewadi et al., 2008). Two large studies by Chen et al. (2008a, 2008b, 2009) of a mixture of 13 Chinese herbs found an improvement on general psychopathology. When kidney yang was added to risperidone, an improvement on cognitive and depressive symptoms was found in one study (from two) (Chen et al., 2008a, 2009). One study found no effect of the Chinese herb sarsasapogenin compared with placebo when added to risperidone on positive, negative, and cognitive symptoms or general psychopathology in 90 patients during 8 weeks (Xiao et al., 2011). Many different nonsevere adverse effects were reported (*e.g.*, gastrointestinal, drowsiness, and insomnia).

(iv) B Vitamins

Nineteen RCTs on B vitamins added to antipsychotics (Ananth et al., 1972, 1973; Deutsch et al., 1977; Godfrey et al., 1990; Hill et al., 2011; Joshi, 1982; Kline et al., 1967; Lerner et al., 2001, 2002, 2004, 2007; Levine et al., 2006; McGrath et al., 1972; Meltzer et al., 1969; Miodownik et al., 2006; Petrie et al., 1981; Ramsay et al., 1970; Roffman et al., 2013; Sacks et al., 1989; Wittenborn et al., 1973) and one on B3 without antipsychotics (Greenbaum 1970) were found. B1 showed some positive effect on general psychopathology (when combined with B6 and B12) in one study (Joshi, 1982) and on positive and negative symptoms in another (Sacks et al., 1989). B3 showed improved general psychopathology in three (from nine) studies (Ananth et al., 1972, 1973; Petrie et al., 1981). B6 improved general psychopathology in four (from five) studies (Ananth et al., 1973; Lerner et al., 2004; Miodownik et al., 2006; Petrie et al., 1981). In one study, general psychopathology improved after the administration of methylfolate (Godfrey et al., 1990). One study reported no effect of B9 (folic acid) (Hill et al., 2011). Another study showed a positive effect of combined B6, B9, and B12 on positive, negative, and cognitive symptoms (Levine et al., 2006). Yet, another study showed improved negative symptoms by adding B9 (folic acid) and B12 to antipsychotics, but only in those with a specific genotype (Roffman et al., 2013). B6 improved extrapyramidal adverse effects of antipsychotics (TD and neuroleptic induced akathisia) in four (from four) studies (Lerner et al., 2001, 2002, 2004, 2007; Miodownik et al., 2006). In one study on B3 in 57 children without antipsychotics, cognition and general psychopathology had not improved after 6 months (Greenbaum, 1970). Most B vitamins induced modest adverse effects, especially skin flushing and abnormal liver function induced by vitamin B3 and B6.

(v) Antioxidants

Two RCTs on vitamin C were found (Bhavani et al., 1962; Dakhale et al., 2005). One reported improved general psychopathology and reduced adverse effects (reduced serum malondialdehyde; a lipid peroxidation product) when added to olanzapine (10 mg), quetiapine (200 mg), or ziprasidone (40 mg) after 8 weeks (Dakhale et al., 2005). One study without antipsychotics found no effect on cognition or motor functioning after 10 days (Bhavani et al., 1962). Both studies reported no adverse effects of vitamin C.

Four studies on ginkgo biloba were found (Zhang et al., 2001a, 2001b, 2006, 2011b; Zhou et al., 1999). Three (from four) studies found improved positive symptoms (Zhang et al., 2001a, 2001b, 2006, 2011b; Zhou et al., 1999), two (from three) found improved general psychopathology (Zhang et al., 2001a; Zhou et al., 1999), and four (from four) reported no improvement of negative symptoms when added to antipsychotics (Zhang et al., 2001a, 2001b, 2006, 2011a; Zhou et al., 1999). In all four studies, adverse effects of antipsychotics improved (behavioral toxicity, symtoms of nervous system, and TD). No adverse effects of ginkgo were reported.

Thirteen studies of vitamin E were found (Adler et al., 1993, 1999; Akhtar et al., 1993; Dabiri et al., 1994; Dorevitch et al., 1997a, 1997b; Egan et al., 1992; Elkashef et al., 1990; Lam et al., 1994; Lohr and Caligiuri, 1996; Salmasi et al., 2009; Schmidt et al., 1991; Shriqui et al., 1992). Six (from 13) studies for reducing EPSs, while using antipsychotics, showed a decrease of TD (Adler et al., 1993; Akhtar et al., 1993; Dabiri et al., 1994; Egan et al., 1992; Elkashef et al., 1990; Lohr and Caligiuri 1996) and EPS (one study; Elkashef et al., 1990), and those with shorter duration of TD seemed to improve more; no adverse effects of vitamin E were reported, except mild diarrhea in two studies. Five (from five) reported no effect on general psychopathology (Adler et al., 1999; Dorevitch et al., 1997a; Elkashef et al., 1990; Lam et al., 1994; Lohr and Caligiuri, 1996). One study of melatonin for TD reported a decrease of TD and no adverse effects (Shamir et al., 2001).

(vi) Other Substances

Agents that did not fit in the five aforementioned categories were classified in this residual category. A total of 16 high-quality RCTs have been performed on multivitamins (Altman et al., 1973; Vaughan and McConaghy, 1999), hormones (DHEA; Nachshoni et al., 2005; Ritsner, 2010; Ritsner et al., 2006; Strous et al., 2003, 2007), pregnenolone (PREG; Ritsner, 2010), estradiol (Akhondzadeh et al., 2003; Kulkarni et al., 2008, 2011), protilerin (thyrotropin-releasing hormone) (Prange, 1979), testosterone (Ko et al., 2008), inositol (Levine et al., 1994), gamma-hydroxybutyrate (GHB; Levy et al., 1983; Schulz et al., 1981) and des-tyr-gamma-endorphin (Verhoeven et al., 1979).

Two (from five) studies on DHEA added to antipsychotics showed improvement of negative symptoms (Ritsner et al., 2006; Strous et al., 2003), two (from three) on positive symptoms (Ritsner, 2010; Ritsner et al., 2006), one (from three) on cognition (Ritsner et al., 2006), two (from two) on depression (Ritsner et al., 2006; Strous et al., 2003), and one (from four) on general functioning (Strous et al., 2003). Three (from four) improved adverse effects of drugs (Nachshoni et al., 2005; Ritsner, 2010; Strous et al., 2007). In one study of 30 patients with schizophrenia, using either 5 g of 1% testosterone gel or a placebo added to a fixed dosage of antipsychotic medication over a period of 4 weeks, negative symptoms improved without adverse effects (Ko et al., 2008). One (from one) small study ($N = 12$) on protilerin found improved general psychopathology (Prange, 1979). Three (from three) studies on estradiol showed improvement of general psychopathology (Akhondzadeh et al., 2003; Kulkarni et al., 2008, 2011), two (from three) of positive symptoms (Akhondzadeh et al., 2003; Kulkarni et al., 2008), one (from one) of improved cognition (Kulkarni et al., 2008), and none (from three) of negative symptoms.

One (from one) small study ($N = 14$) on inositol found no effect on positive or negative symptoms (Levine et al., 1994). Two (from two) studies on GHB found no improvement of general psychopathology (Levy et al., 1983; Schulz et al., 1981). One (from one) very small ($N = 6$) study on des-tyr-gamma-endorphin found improvement on general psychopathology and positive symptoms (Verhoeven et al., 1979). No serious adverse effects of these agents were reported.

One study (of two) on artemisinin (a natural medicine against malaria) found a significant effect on negative symptoms and clinical global impression, but no effect on positive or cognitive symptoms or on general psychopathology in first-episode treatment-naive patients that were treated with risperidone (Dickerson et al., 2011; Wang et al., 2014). The study of Dickerson et al. (2011) did not demonstrate clinical benefit of adjunctive artemisinin for schizophrenia symptoms.

DISCUSSION

This review describes the effects of natural agents in the treatment of psychotic disorders and of undesired effects of antipsychotics. Some studies suggest that glycine, sarcosine, NAC, several Chinese and ayurvedic herbs, ginkgo biloba, estradiol, and vitamin B6 may be effective for psychotic symptoms when added to antipsychotics (glycine not when added to clozapine). We found inconclusive or no evidence for omega-3 fatty acids, D-serine, D-alanine, D-cycloserine, other B vitamins, vitamin C, DHEA, PREG, inositol, GHB, and des-tyr-gamma-endorphin when added to antipsychotics. Reserpine without antipsychotics seemed effective in one old study but was poorly tolerated. Ayurvedic herbs seemed equally effective as olanzapine in only one study. Other agents as monotherapy (vitamin B3, vitamin C, sarcosine, glycine, and protilerin) were not effective or had only been tested in single or small trials. For alleviation of adverse effects, ginkgo and vitamin B6 seemed effective for TD and neuroleptic induced akathisia (NIA). The evidence for reducing some adverse effects of antipsychotics by omega-3 fatty acids, melatonin, and DHEA was inconclusive.

Apart from reserpine, all natural compounds studied caused no or mild undesired adverse effects. There is inconclusive evidence for improved outcome by combining omega-3 fatty acids with antipsychotics in schizophrenia. Earlier reviews reported similar conclusions (Boskovic et al., 2011; Irving et al., 2006; Tsalamanios et al., 2006). A meta-analysis of randomized placebo controlled trails showed a modest, non-significant, beneficial effect of fatty acids in schizophrenia (Fusar-Poli and Berger, 2012).

Glycine and sarcosine combined with antipsychotics may reduce negative symptoms, but not when combined with clozapine and neither as monotherapy. Inconclusive evidence was found for D-cycloserine and D-serine on clinical improvement. Our results concur with two reviews (Singh and Singh, 2011; Tsai and Lin, 2010) and are in line with a Cochrane review (Tiihonen and Wahlbeck, 2006). Conflicting results from studies on drugs targeting the glutamate/NMDA system may be explained by complicated dose-effect relationships, as recently found in studies with the GlyT-1 transporter antagonist bitopertin (Umbricht et al., 2013).

By adding Chinese or ayurvedic herbs to antipsychotics, general psychopathology may improve. One study (of two) on artemisinin (a natural medicine against malaria) found a significant effect on negative symptoms and clinical global impression, but no effect on positive or cognitive symptoms or on general psychopathology in first-episode treatment-naive patients who were treated with risperidone (Wang et al., 2014; Dickerson et al., 2011). The study of Dickerson et al. (2011) did not demonstrate clinical benefit of adjunctive artemisinin for schizophrenia symptoms. Rathbone et al. (2007) state that "the results suggest that combining Chinese herbal medicine with antipsychotics is beneficial." Another Cochrane review (Agarwal et al., 2007) concludes that "ayurvedic medication may have some effects for treatment of schizophrenia, but has been evaluated only in a few small pioneering trials." These results need further exploration and pharmacological differentation, as Chinese and ayurvedic herbs include hundreds of species combined in thousands of different combinations and are prescribed in a fundamentally different way than Western medicines (Clifford, 1994; Kaptchuck, 2000). The combined approach using knowledge from both conventional and Chinese medicine seems promising, as it may lead to innovation (Van der Greef, 2011) and possibly to improved outcomes (Zhang et al., 2011b).

Inconsistent beneficial outcomes of studies on B vitamins were identified, especially when given as a combination of B1, B3, B6, B9, and/or B12 with antipsychotics. One review concluded that no adequate support for the efficacy of B vitamins in schizophrenia can be identified (Kleijnen and Knipschild, 1991). Most studies with positive effects in our review, however, were published after the aforementioned review was published. Most convincing evidence was found for vitamin B6 added to antipsychotics, shown to be effective in diminishing general psychopathology and TD.

The findings on the efficacy of vitamin C for schizophrenia in only two RCTs were inconsistent, hindering definite conclusions. The efficacy of vitamin E on TD remains inconclusive, as only half of the included studies found some positive results. Even so, a meta-analysis by Boskovic et al. (2011) claimed, "Vitamin E could potentially improve TD." This may be due to the finding that those with a short history of TD tend to improve more than those with a longer history of TD. A Cochrane review in 2011 (Soares et al., 2011) came to a similar conclusion: "small trials of limited quality suggest that vitamin E may protect against deterioration of TD. There is no evidence that vitamin E improves symptoms of this problematic and disfiguring condition once established."

Ginkgo biloba seems to benefit patients with schizophrenia in several ways when added to antipsychotics. Several studies suggested evidence for improving symptoms in various domains, especially an effect on positive symptoms and the reduction of adverse effects of antipsychotics.

On melatonin, one study provided preliminary evidence for diminishing TD (Shamir et al., 2001). As TD is difficult to investigate because of the fluctuating symptom severity, this study needs replication.

Some inconsistent evidence was found on improved outcomes by several hormones (DHEA, PREG, and testosterone) in schizophrenia, not allowing final conclusions. A Cochrane review on DHEA/testosterone drew a similar conclusion (Elias and Kumar, 2007). For estradiol, a Cochrane review reported no convincing evidence over placebo (Chua et al., 2005). Since then, two studies found that estradiol improves positive (but not negative) symptoms and general psychopathology in schizophrenia when added to antipsychotics (Kulkarni et al., 2008, 2011), however only in women of childbearing age. Therefore, using estradiol in schizophrenia warrants further study.

Limitations

There are several methodological limitations. First, the wide scope of this review allows only general descriptions of included studies in six domains. Second, it is unclear to which extent our findings are influenced by publication bias, in favor of publication of studies with positive results. Third, we used the Jadad score to select only RCTs of high quality (with a score of three or higher, as is in accordance with other reviews [*e.g.*, see Thirthalli et al., 2016]). However, the Jadad score is not a perfect tool because it does not judge the selection of subjects, the sample size and power, and the quality of the data analyses. Therefore, RCTs with a Jadad score of 3 or higher might still have methodological weaknesses, which hamper drawing firm conclusions. Fourth, some studies (*e.g.*, Bhavani et al., 1962; Greenbaum 1970; Naidoo, 1956) were done in the pre–*Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition* (*DSM-3*) era, when standards of care and diagnostics may have been of lower quality than nowadays, which hampers interpretation of their results. Fifth, in most of the studies included, effect sizes were not provided nor was it possible to calculate them, which makes it difficult to compare the results or to estimate the clinical relevance of some of the findings. Sixth, it cannot be ruled out that some of the studies were underpowered, which might have hampered finding a significant effect.

Clinical Implications

Clinicians need to be aware that patients often use natural medicines without medical prescription, whereas some patients assume that natural is better than chemical and causes fewer adverse effects. Although beneficial effects may occur, this is certainly not always true. Some natural agents that may be suggested for treatment of psychotic disorders are toxic to humans (Topliss et al., 2002), and some herbal medicines can cause adverse effects or interact with medication (Ernst, 2003b). Only 3% of the user population is aware of the potential risks of interactions between herbs and prescription medication (Walter and Rey, 1999). From a medical perspective, it is therefore important to know what patients buy and try. Another concern are the media reports on contamination of Chinese herbs with heavy metals. However, after investigation of 334 samples, Harris et al. (2011) conclude that "the vast majority (95%) of medications in this study contained levels of heavy metals or pesticides that would be of negligible concern." Because of these concerns, patients want their medical doctors to advise them on complementary (or natural) medicines (Gray et al., 1998; Hoenders et al., 2006). The World Health Organization (2013) has repeatedly advised its member states to "formulate national policy and regulation for the proper use of CAM and its integration into national health care systems; establish regulatory mechanisms to control the safety and quality of products and of CAM practice; create awareness about safe and effective CAM therapies among the public and consumers" and "promote therapeutically sound use of appropriate Traditional Medicine by practitioners and consumers." Respecting patients' opinions and informing them may also improve the therapeutic relationship (Stevinson, 2001) and thus enhance treatment outcome (Gill, 2013; Koenig, 2000), which depends on the quality of the therapeutic alliance (Baldwin et al., 2007).

This review gives clinicians and patients an overview of the results of RCTs, which fit a minimal level of quality (minimum Jadad score of 3), on the efficacy and safety of natural medicines for psychotic disorders. However, many questions about clinical use (*e.g.*, dosage, safety, interactions, and quality) remain unanswered.

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DISCLOSURE

The authors declare no conflict of interest.

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