Adjunctive agents to antipsychotics in schizophrenia: A systematic umbrella review and recommendations for amino acids, hormonal therapies, and anti-inflammatory drugs

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Supplementary material 1. Detailed methodology for expert meetings, literature searches, inclusion criteria, data extraction and risk of bias assessment.

1. Expert meetings

A series of six expert meetings were organized by the French Schizophrenia Expert Center Network (foundation FondaMental) between January 2022 and June 2022 (once a month, 2-hour long each). The agents were selected if there were at least three RCTs and one meta-analysis published on it. In these meetings, two to three experts who conducted a systematic umbrella review, presented their conclusions to the whole expert network on one or two adjunctive agents for the treatment of schizophrenia. Levels of evidence were determined according to the criteria of the Scottish Intercollegiate Guidelines Network (SIGN) [1] for each individual RCT as recommended by the WFSBP [2]. A methodological meeting was organized to harmonize the quality rating of the working groups. In case of doubt, the raters were requested to choose the most favorable level of evidence to avoid any over-interpretation of the results. In case of non-consensus for one level of evidence, a consensus meeting with at least three authors was carried out (the two leading authors the first author). All expert clinicians and clinician researchers discussed the final results during the meeting sessions of the French Expert Schizophrenia Center Network. These data were then synthetized in an umbrella meta-review following WFSBP-grade recommendations [50]; importantly this method should not be confounded with the GRADE system [53].

As many molecules were only studied in few RCTs (much less than antipsychotics in comparison), we changed the wording from “strong recommendation” (corresponding to the WFSBP-grade 1 level) to “strong provisional recommendation” to indicate that further RCTs may have a high potential to modify the present recommendations (hence, provisional also applies to moderate and weak recommendations). According to WFSBP guidelines, “acceptability” ratings consider the following aspects: risk-benefit ratio (e.g., adverse effects, interactions), cost-benefit ratio, applicability in the target population, ethical and legal aspects, preferences of service users, and practicability” [2].

International experts were then contacted. The international expert was defined as a non-French expert who actively participated in a meta-analytic work including at least one of the molecules evaluated in the review or with an experience of graded recommendations or assessment of the risk of bias combined with being clinically active in treating patients with schizophrenia. The experts were asked to review and validate the conclusions of the selected and reviewed agents. This panel includes 9 experts (MB, MEB, MB, CUC, MF, JK, MS, IES, SMS). All molecules reached

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consensus at the first step except hormonal therapies, for which there was a debate on safety. Recommendations for hormonal therapies were therefore downgraded.

2. Literature searches

Medline®, Cochrane®, Clinicaltrials.gov[1], EU Clinical Trials Register[2] databases were searched from their inception. The search paradigm was developed for Medline® and adapted for other databases: "schizophrenia or schizo-affective disorder or (first-episode psychosis) or (psychotic disorder)[Title/Abstract]" was combined with the following terms: (aspirin[Title/Abstract] OR celecoxib[Title/Abstract] "anti-inflammatory drugs"[Title/Abstract] OR N-acetyl-cysteine[Title/Abstract] OR NAC[Title/Abstract] OR raloxifen[Title/Abstract] OR estrogen[Title/Abstract] OR PUFA[Title/Abstract] OR omega-3[Title/Abstract] OR sarcosine[Title/Abstract] OR minocycline[Title/Abstract])), with a filter for randomized controlled trials, systematic reviews and meta-analyses. The references were manually searched to recover potentially missed RCTs

3. Inclusion criteria

Participants. Patients with schizophrenia, schizo-affective disorder, schizophreniform disorder and first-episode schizophrenia in stabilized or acute phase, in and outpatients.

Interventions. The adjunctive agents with at least three randomized controlled trials (RCTs) and one meta-analysis were included in the present work, and a leading author (or a pair/triad of leading authors) was convened on a voluntary basis to extract this data in a preform sheet and to rate the risk of bias. The choice to limit the work to agents with at least three RCTs was based on the GRADE recommendations, which suggests that at least three RCTs are necessary to conclude on effectiveness/ineffectiveness with the highest degree of confidence (Level Of Evidence (LoE)= A or -A)[3] and to limit the size of the work to the drugs with the most advanced evidence. The included agents (and reviewers) were (in order of decreasing evidence/number of RCTs): N-acetyl-cysteine (leading authors: FB and GF), minocycline (RR, HT and FB), poly-unsatured fatty acids (PUFAs) (MU, DM and GF), estrogens (JM and GF), Selective estrogen receptor modulators (SERM)(BP and FB), celecoxib (FB and GF), aspirin (FS and GF), sarcosine (GF and FB).

The main outcomes were: effectiveness on positive symptoms, negative symptoms, general psychopathology (here referring to as the symptoms included in the PANSS-G subscale), total psychotic symptomatology and cognition (with any laboratory test but not with clinical scales like the PANSS cognitive factor). Secondary outcomes included adverse effects, all-cause of discontinuation (acceptability) and discontinuation due to adverse effects.

4. Data extraction

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The following data were extracted by at least two authors: Study ID, country, Study population, Setting, Coinitiation or augmentation (antipsychotic treatment, flexible/fixed doses), total sample size (N treatment, N placebo), Dose of adjunctive treatment (mg/day), trial duration (weeks), effect on positive symptoms, negative symptoms, general psychopathology, total psychotic symptomatology and cognition (three modalities: significant improvement ("+"), non-significant effect ("ns") or significant worsening ("-")). For cognition, if some tests provided significant improvement and other non-significant results, "+/ns" was noted. If one test only was positive with a p value at the limit of significance (e.g. 0.04) with all other tests non-significant, this effect was attributed to multiple testing and the results were reported as non-significant (ns).

5. Subgroups

As the RCTs were heterogenous, we created some subgroups of the RCTs to determine if some precision-medicine recommendations could be provided. These subgroups were : first-episode schizophrenia/early-phase schizophrenia, chronic schizophrenia, stabilized schizophrenia, acute phase schizophrenia, augmentation design (i.e., adjunctive treatment added to stabilized antipsychotic), co-initiation design (i.e., in an acute phase), patients treated with clozapine, patients treated with other antipsychotics than clozapine (as clozapine is a proxy for treatment-resistant schizophrenia), trials including women only or men only, and childbearing-age women and post-menopausal women (these two last groups for hormonal therapy only).

Two studies explicitly reported that patients had predominant negative symptoms because the agents (here minocycline[4], and sarcosine[5]) were specifically tested for their effectiveness on negative symptoms. Thirty-three studies (52.4%) explicitly reported that patients had symptoms scoring above a certain cut-off (see Table SM4, column 3 "Study population").

As some authors have suggested that results may vary between high- and middle-income countries[6], we conducted additional sensitivity analyses in which we examined whether the probability of finding positive results was higher in upper middle-income countries compared to high-income countries. Upper middle-income countries were: China, India, Iran, Romania/Moldova, South Africa; high-income countries were: Australia, Norway, Poland, Spain, South Korea, Switzerland, the UK, and the USA[7].

Twenty-seven out of the included studies (42.9%) were carried out in upper middle-income countries (China, Iran, Romania, South Africa). Among the 24 studies with a low risk of bias, 12 (50.0%) were carried out in upper middle-income countries.

6. Risk of bias assessment

Levels of evidence were determined according to the criteria of the Scottish Intercollegiate Guidelines Network (SIGN)[8] as recommended in the World Journal of Biological Psychiatry

guidelines[3]. The following forms were fulfilled by each leading author for each RCT and meta-analysis (**Supplementary Material 2)**.

A study was classified as “low risk of bias” if it was rated “high quality” according to SIGN criteria AND if the total sample size was ≥30 AND if there were no conflicts of interest. A study was classified as “moderate risk of bias” if it was rated “acceptable” on the SIGN criteria OR if there were conflicts of interest AND if the total sample size was ≥30. A study was classified as “high risk of bias” if it was rated “low quality” on the SIGN criteria OR if the total sample size was <30.

7. Main outcomes

The main outcomes were: effectiveness on positive symptoms, negative symptoms, general psychopathology, total psychotic symptomatology and cognition. Secondary outcomes included adverse effects, safety issues, all-cause of discontinuation (a proxy for acceptability) and discontinuation due to adverse effects. The last investigation was carried out on February 28, 2022.

Supplementary material 2. Characteristics of the 29 meta-analyses with their risk of bias.

	Year	Study ID	N-acetyl-cysteine	Sarcosine	Minocycline	PUFAs	Estrogens	SERM	Aspirin	Celecoxib	Risk of bias
Mixed adjunctive drugs											
	2014	Sommer IE, van Westrhenen R, Begemann MJH, de Witte LD, Leucht S, Kahn RS. Efficacy of Anti-inflammatory Agents to Improve Symptoms in Patients With Schizophrenia: An Update. *Schizophr Bull*. 2014;40(1):181-191. doi:10.1093/schbul/sbt139	1		4	7	7		2	5	Low
	2019	Çakici N, van Beveren NJM, Judge-Hundal G, Koola MM, Sommer IEC. An update on the efficacy of anti-inflammatory agents for patients with schizophrenia: a meta-analysis. *Psychol Med*. 2019;49(14):2307-2319. doi:10.1017/S0033291719001995	5		12	14	6	5	2	5	Low
	2019	Cho M, Lee TY, Kwak YB, Yoon YB, Kim M, Kwon JS. Adjunctive use of anti-inflammatory drugs for schizophrenia: A meta-analytic investigation of randomized controlled trials. *Aust N Z J Psychiatry*. 2019;53(8):742-759. doi:10.1177/0004867419835028	2		5	12	7	9	2	4	Moderate
	2019	Chang CH, Lane HY, Tseng PT, Chen SJ, Liu CY, Lin CH. Effect of N-methyl-D-aspartate-receptor-enhancing agents on cognition in patients with schizophrenia: A systematic review and meta-analysis of double-blind randomised controlled trials. *J Psychopharmacol Oxf Engl*. 2019;33(4):436-448. doi:10.1177/0269881118822157	2		3						Moderate
	2020	Jeppesen R, Christensen RHB, Pedersen EMJ, et al. Efficacy and safety of anti-inflammatory agents in treatment of psychotic disorders - A comprehensive systematic review and meta-analysis. *Brain Behav Immun*. 2020;90:364-380. doi:10.1016/j.bbi.2020.08.028	7		8	14	6	7	2	3	low
N-acetylcysteine											
	2016	Magalhães PVS, Dean O, Andreazza AC, Berk M, Kapczinski F. Antioxidant treatments for schizophrenia. Cochrane Schizophrenia Group, ed. *Cochrane Database Syst Rev*. Published online February 5, 2016. doi:10.1002/14651858.CD008919.pub2	2								Moderate
	2018	Zheng W, Zhang QE, Cai DB, et al. N-acetylcysteine for major mental disorders: a systematic review and meta-analysis of randomized controlled trials. *Acta Psychiatr Scand*. 2018;137(5):391-400. doi:10.1111/acps.12862	6								Moderate
	2020	Yolland CO, Hanratty D, Neill E, et al. Meta-analysis of randomised controlled trials with N-acetylcysteine in the treatment of schizophrenia. *Aust N Z J Psychiatry*. 2020;54(5):453-466. doi:10.1177/0004867419893439	7								Low
Sarcosine											
	2010	Tsai GE, Lin PY. Strategies to enhance N-methyl-D-aspartate receptor-mediated neurotransmission in schizophrenia, a critical review and meta-analysis. *Curr Pharm Des*. 2010;16(5):522-537. doi:10.2174/138161210790361452		3							Moderate

	Year	Study ID	N-acetyl-cysteine	Sarcosine	Minocycline	PUFAs	Estrogens	SERM	Aspirin	Celecoxib	Risk of bias
	2011	Singh SP, Singh V. Meta-analysis of the efficacy of adjunctive NMDA receptor modulators in chronic schizophrenia. *CNS Drugs*. 2011;25(10):859-885. doi:10.2165/11586650-000000000-00000		4							Low
	2020	Chang CH, Lin CH, Liu CY, Chen SJ, Lane HY. Efficacy and cognitive effect of sarcosine (N-methylglycine) in patients with schizophrenia: A systematic review and meta-analysis of double-blind randomised controlled trials. *J Psychopharmacol Oxf Engl*. 2020;34(5):495-505. doi:10.1177/0269881120908016		7							Moderate
	2021	Marchi M, Galli G, Magarini FM, Mattei G, Galeazzi GM. Sarcosine as an add-on treatment to antipsychotic medication for people with schizophrenia: a systematic review and meta-analysis of randomized controlled trials. *Expert Opin Drug Metab Toxicol*. 2021;17(4):483-493. doi:10.1080/17425255.2021.1885648		6							Moderate
	2021	Goh KK, Wu TH, Chen CH, Lu ML. Efficacy of N-methyl-D-aspartate receptor modulator augmentation in schizophrenia: A meta-analysis of randomised, placebo-controlled trials. *J Psychopharmacol Oxf Engl*. 2021;35(3):236-252. doi:10.1177/0269881120965937		6							Moderate
Minocycline											
	2014	Oya K, Kishi T, Iwata N. Efficacy and tolerability of minocycline augmentation therapy in schizophrenia: a systematic review and meta-analysis of randomized controlled trials. *Hum Psychopharmacol*. 2014;29(5):483-491. doi:10.1002/hup.2426			4						Moderate
	2017	Solmi M, Veronese N, Thapa N, et al. Systematic review and meta-analysis of the efficacy and safety of minocycline in schizophrenia. *CNS Spectr*. 2017;22(5):415-426. doi:10.1017/S1092852916000638			6						Low
	2017	Xiang YQ, Zheng W, Wang SB, et al. Adjunctive minocycline for schizophrenia: A meta-analysis of randomized controlled trials. *Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol*. 2017;27(1):8-18. doi:10.1016/j.euroneuro.2016.11.012			8						Moderate
	2019	Zheng W, Zhu XM, Zhang QE, et al. Adjunctive minocycline for major mental disorders: A systematic review. *J Psychopharmacol Oxf Engl*. 2019;33(10):1215-1226. doi:10.1177/0269881119858286			13						Moderate
Poly-unsaturated fatty acids (PUFAs)											
	2006	Joy CB, Mumby-Croft R, Joy LA. Polyunsaturated fatty acid supplementation for schizophrenia. *Cochrane Database Syst Rev*. 2006;(3):CD001257. doi:10.1002/14651858.CD001257.pub2				8					Low
	2012	Fusar-Poli P, Berger G. Eicosapentaenoic acid interventions in schizophrenia: meta-analysis of randomized, placebo-controlled studies. *J Clin Psychopharmacol*. 2012;32(2):179-185. doi:10.1097/JCP.0b013e318248b7bb				7					Low
	2015	Chen AT, Chibnall JT, Nasrallah HA. A meta-analysis of placebo-controlled trials of omega-3 fatty acid augmentation in schizophrenia: Possible stage-specific				10					Moderate

	Year	Study ID	N-acetyl-cysteine	Sarcosine	Minocycline	PUFAs	Estrogens	SERM	Aspirin	Celecoxib	Risk of bias
		effects. *Ann Clin Psychiatry Off J Am Acad Clin Psychiatr*. 2015;27(4):289-296.									
	2021	Goh KK, Chen CYA, Chen CH, Lu ML. Effects of omega-3 polyunsaturated fatty acids supplements on psychopathology and metabolic parameters in schizophrenia: A meta-analysis of randomized controlled trials. *J Psychopharmacol Oxf Engl*. 2021;35(3):221-235. doi:10.1177/0269881120981392				17					Moderate
Estrogens and Selective estrogen receptor modulators (SERM)											
	2012	Begemann MJH, Dekker CF, van Lunenburg M, Sommer IE. Estrogen augmentation in schizophrenia: a quantitative review of current evidence. *Schizophr Res*. 2012;141(2-3):179-184. doi:10.1016/j.schres.2012.08.016					5				Low
	2018	Zhu XM, Zheng W, Li XH, et al. Adjunctive raloxifene for postmenopausal women with schizophrenia: A meta-analysis of randomized, double-blind, placebo-controlled trials. *Schizophr Res*. 2018;197:288-293. doi:10.1016/j.schres.2018.01.017						5			Moderate
	2018	de Boer J, Prikken M, Lei WU, Begemann M, Sommer I. The effect of raloxifene augmentation in men and women with a schizophrenia spectrum disorder: a systematic review and meta-analysis. *NPJ Schizophr*. 2018;4(1):1. doi:10.1038/s41537-017-0043-3						9			Low
	2018	Wang Q, Dong X, Wang Y, Li X. Raloxifene as an adjunctive treatment for postmenopausal women with schizophrenia: a meta-analysis of randomized controlled trials. *Arch Womens Ment Health*. 2018;21(1):31-41. doi:10.1007/s00737-017-0773-2						6			Moderate
COX inhibitors											
	2012	Sommer IE, de Witte L, Begemann M, Kahn RS. Nonsteroidal anti-inflammatory drugs in schizophrenia: ready for practice or a good start? A meta-analysis. *J Clin Psychiatry*. 2012;73(4):414-419. doi:10.4088/JCP.10r06823							1	4	Low
	2013	Nitta M, Kishimoto T, Müller N, et al. Adjunctive use of nonsteroidal anti-inflammatory drugs for schizophrenia: a meta-analytic investigation of randomized controlled trials. *Schizophr Bull*. 2013;39(6):1230-1241. doi:10.1093/schbul/sbt070							2	6	Low
	2017	Zheng W, Cai DB, Yang XH, et al. Adjunctive celecoxib for schizophrenia: A meta-analysis of randomized, double-blind, placebo-controlled trials. *J Psychiatr Res*. 2017;92:139-146. doi:10.1016/j.jpsychires.2017.04.004								8	Moderate
	2021	Weiser M, Zamora D, Levi L, et al. Adjunctive Aspirin vs Placebo in Patients With Schizophrenia: Results of Two Randomized Controlled Trials. *Schizophr Bull*. 2021;47(4):1077-1087. doi:10.1093/schbul/sbaa198							4		Low

Supplementary material 3. Methodology Checklist : Controlled Trials.

SIGN	Methodology Checklist : Controlled Trials

Study identification (*Include author, title, year of publication, journal title, pages*)

Guideline topic:	Key Question No:	Reviewer:

Before completing this checklist, consider:

1. Is the paper a **randomised controlled trial** or a **controlled clinical trial**? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist. If it is a **controlled clinical trial** questions 1.2, 1.3, and 1.4 are not relevant, and the study cannot be rated higher than 1+
2. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist.

Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

Section 1: Internal validity

In a well conducted RCT study…		Does this study do it?
1.1	The study addresses an appropriate and clearly focused question.	Yes ☐ No ☐ Can't say ☐
1.2	The assignment of subjects to treatment groups is randomised.	Yes ☐ No ☐ Can't say ☐
1.3	An adequate concealment method is used.	Yes ☐ No ☐ Can't say ☐
1.4	The design keeps subjects and investigators 'blind' about treatment allocation.	Yes ☐ No ☐ Can't say ☐
1.5	The treatment and control groups are similar at the start of the trial.	Yes ☐ No ☐ Can't say ☐
1.6	The only difference between groups is the treatment under investigation.	Yes ☐ No ☐ Can't say ☐
1.7	All relevant outcomes are measured in a standard, valid and reliable way.	Yes ☐ No ☐ Can't say ☐
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis).	Yes ☐ No ☐ Can't say ☐ Does not apply ☐

1.10	Where the study is carried out at more than one site, results are comparable for all sites.	Yes ☐ Can't say ☐	No ☐ Does not apply ☐

Supplementary material 4. PRISMA Checklist.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	P1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	P3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	P4-P5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	P5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	SM1
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	SM1
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	SM1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	P5+SM1
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	P5+SM1
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	P5-P6+SM1
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	P5-P6+SM1
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	SM1
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	SM1
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	SM1
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	SM1
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	SM1
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	SM1
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	P5/6+SM1
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	P5/6+SM1

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	SM1
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	SM1
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	P6+SM2
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	P6+SM2
Study characteristics	17	Cite each included study and present its characteristics.	P6+SM2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	SM1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	NA
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	P6-13+SM2
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	P6-13+SM2
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	P6-13+SM2
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	P6-13+SM2
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	P6-13+SM2
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	P6-13+SM2
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	P13-17
	23b	Discuss any limitations of the evidence included in the review.	P13-17
	23c	Discuss any limitations of the review processes used.	P13-17
	23d	Discuss implications of the results for practice, policy, and future research.	P13-17
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	P18

Section and Topic	Item #	Checklist item	Location where item is reported
Competing interests	26	Declare any competing interests of review authors.	P18
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71
For more information, visit: http://www.prisma-statement.org/

Supplementary material 5. Characteristics of the 63 randomized controlled trials (RCTs) with their risk of bias.

Study ID	Country	Study population	Setting	Coinitiation or augmentation (antipsychotic treatment, flexible/fixed doses)	N	Dose (mg/day)	Duration (weeks)	Positive symptoms PANSS-P	Negative symptoms PANSS-N	General psychopathology PANSS-G	Total psychotic symptoms PANSS-T	Cognition	Risk of bias
N-acetyl-cysteine (NAC). 8 RCTs. N total=523, N NAC=258, N placebo=265													
Early-phase schizophrenia													
Conus et al. (2018)	**Switzerland**	**Early psychosis**	**Outpatients**	Augmentation **(FGA + SGA, flexible dose)**	**61 (31 vs 30)**	**2700**	**26**	**ns**	**ns**	**ns**	**ns**	**+/ns**	**Low**
Breier et al. (2018)	USA	Early schizophrenia	Outpatients	Augmentation (FGA + SGA, flexible dose)	32 (14 vs 18)	600-3600 titrate	52	ns	+	ns	+	ns	Moderate
Davis et al. (2014)	USA	Early and chronic schizophrenia	Outpatients	Augmentation (FGA + SGA, unspecified flexible dose)	17 (8 vs 9)	1200	8	ns	ns	ns	ns	ns	Moderate
Chronic schizophrenia													
Berk et al. (2008)	Australia	Chronic schizophrenia	Outpatients	Augmentation (FGA + SGA, flexible dose)	139 (68 vs 71)	2000	24	ns	+	+	+	NA	Moderate
Rapado-Castro et al. (2017)	Australia	Chronic schizophrenia	Outpatients	Augmentation (FGA + SGA, flexible dose)	32 (15 vs 17)	2000	24	NA	NA	NA	NA	+/ns	Moderate
Sepehrmanesh et al. (2018)	**Iran**	**Chronic schizophrenia**	**Outpatients**	**Augmentation (FGA + SGA + anti-cholinergic agents, fixed dose)**	**79 (40 vs 39)**	**1200**	**12**	**+**	**+**	**+**	**+**	**+/ns**	**Low**
Acute phase													
Zhang et al. (2015)	China	First episode	NA	Coinitiation (risperidone)	121 (61 vs 60)	600	8	+	+	NA	+	NA	High
Farokhnia et al. (2013)	**Iran**	**Chronic schizophrenia**	**Inpatients**	**Coinitiation (risperidone flexible dose)**	**42 (21 vs 21)**	**1000-2000 titrate**	**8**	**ns**	**+**	**ns**	**+**	**NA**	**Low**

Sarcosine, 6 RCTs. N total=211. N sarcosine= 104. N placebo= 107													
Chronic schizophrenia													
Tsai et al. 2004	Taiwan	Chronic schizophrenia Comorbid major depressive episode excluded	In and outpatients	Augmentation (FGA + SGA, fixed dose, stable at least for 3 months, one patient untreated)	36 (16 vs 20)	2000	6	+	+	+	+	NA	High
Lane et al. 2010	Taiwan	Unremitted chronic schizophrenia (PANSS>60) 18-60 years without abnormal biochemical test History of substance abuse, excluded	Inpatients	Augmentation (SGA, fixed dose, stable at least for 3 months)	35 (19 vs 16)	2000	6	NA	+	NA	+	NA	Moderate
Lin et al. 2015	Taiwan	Unremitted chronic schizophrenia (PANSS>60) 18-60 years without abnormal biochemical test History of substance abuse, excluded	Inpatients	Augmentation (SGA, fixed dose, stable at least for 2 months)	32 (16 vs 16)	2000	12	ns	ns	ns	ns	+/ns	Moderate
Strzelecki et al. 2015	Poland	Schizophrenia with dominant negative symptoms, acute psychosis and suicidal ideations excluded 18–60 years	Outpatients	Augmentation (FGA + SGA excluding clozapine, fixed dose, stable at least for 3 months)	50 (25 vs 25)	2000	24	NA	+	NA	+	NA	Moderate
Treatment-resistant schizophrenia													
Lane et al. (2006)	**Taiwan**	Resistant chronic schizophrenia (PANSS>70) Comorbid major depressive episode excluded	Inpatients	Augmentation (Clozapine, fixed dose, stable for at least 3 months)	20 (10 vs 10)	2000	6	ns	ns	ns	ns	ns	High
Acute phase													
Lane et al. (2005)	Taiwan	Chronic schizophrenia (PANSS>60)	Inpatients	Coinitiation (Risperidone, flexible dose)	38 (18 vs 20)	2000	6	ns	+	+	+	NA	Moderate

		18-60 years without abnormal biochemical test History of substance abuse and smokers excluded											
Minocycline 8 RCTs, N total=583, N minocycline=298, N placebo=285													
Early-phase schizophrenia													
Chaudhry et al. (2012)	Brazil & Pakistan	Early schizophrenia spectrum disorder (≤5 years of illness duration) Stable medication > 4 weeks	In- and outpatients	Augmentation (SGA+FGA unspecified, flexible dose unspecified)	94 (46 vs 48)	50-200 titrate within 8 weeks	52	ns	+	ns	ns	ns	Moderate
Liu et al. (2014)	China	Early Schizophrenia (≤5 years of illness duration)	Outpatients (unspecified)	Augmentation (Risperidone, fixed dose)	63 (30 vs 33)	200	16	ns	+	ns	+	ns	Moderate
Deakin et al. (2018)	**UK**	**First episode schizophrenia, schizoaffective or schizophreniform disorder (≤5 years of illness duration) PANSS positive items >2 (P1 delusions, P2 conceptual disorganisation, P3 hallucinatory behaviour, or P6 suspiciousness)**	**Outpatients**	**Augmentation (FGA and SGA, fixed dose)**	**89 (41 vs 48)**	**300 (200 for 2 weeks, then 300)**	**52**	**ns**	**ns**	**ns**	**ns**	**NA**	**Low**
Chronic schizophrenia													
Khodaie-Ardakani et al. (2014)	**Iran**	**Chronic schizophrenia >2 years of illness duration stable dose of risperidone for > 8 weeks clinically stable for > 4 weeks patients with depression excluded**	**Outpatients**	**Augmentation (Risperidone, flexible dose)**	**38 (20 vs 18)**	**200 (100 for 1 week then 200)**	**8**	**ns**	**+**	**+**	**+**	**NA**	**Low**
Resistant schizophrenia													
Kelly et al. (2015)	**USA**	**Chronic schizophrenia or schizoaffective disorder**	**In- and outpatients**	**Augmentation (clozapine, fixed dose)**	**50 (27 vs 23)**	**200**	**10**	**ns**	**ns**	**ns**	**ns**	**ns**	**Low**

		clozapine for >6 months, >200 mg/day, >350 ng/ml (BPRS >= 45 OR CGI >= 4) AND BPRS-P > 8				**(100 for 1 week, then 200)**						
Acute phase													
Levkovitz et al. (2010)	Israel	Early schizophrenia (≤5 years of first antipsychotic exposure) PANSS > 60 Antipsychotic initiation =< 14 days Exclusion of patients with > 25% improvement after the placebo lead-in phase	In- and outpatients (unspecified)	Coinitiation (SGA including clozapine, flexible dose)	12 (13 vs 8)	200	22 Preceeded by a 2 weeks lead-in phase	ns	+ (SANS) / ns (PANSS-N)	ns	ns	+/-	High
Zhang et al. (2018) (3 arms)	**China**	**Chronic schizophrenia PANSS-N > 20; at least one PANSS-N item >= 4; PANSS-N > PANSS-P; PANSS-P, duration of illness from 2-10 years antipsychotic free for >= 2 weeks**	**In- and outpatients**	**Coinitiation (Risperidone, flexible dose 3 to 6 mg)**	**37 (18 (200mg/day) vs 19)** **39 (20(100mg/day) vs 19)**	**200** **100**	**12** **12**	**Ns** **ns**	**+** **ns**	**Ns** **ns**	**Ns** **ns**	**NA** **NA**	**Low** **Low**
Weiser et al. (2019)	Romania & Moldova	Chronic schizophrenia or schizoaffective disorder Use of antipsychotics for >= 2 weeks (>= 2 episodes, duration of illness > 6 months, PANSS-P P1, P2, P3, P6 >= 4 and/or PANSS-N >=18 and CGI >= 4)	In- and outpatients	Coinitiation (SGA+FGA unspecified, flexible dose unspecified)	171 (83 vs 88)	200	16	ns	ns	ns	ns	ns	Moderate
PUFAS, 14 RCTs, N total=809, N PUFA=432, N placebo=377													
Chronic schizophrenia													

Fenton et al., (2001)	USA	Chronic schizophrenia Presence of significant residual symptoms (defined as either one or more positive and/or negative symptom scores > 4 or PANSS total scores greater than 45 with a score of three or greater on at least three positive or negative items)	Outpatients	Augmentation (FGA or SGA, fixed dose)	75 (37 vs 38)	EPA 3000	16	ns	ns	ns	ns	ns	Moderate
Peet et al., 2001 (UK)	United Kingdom	Chronic schizophrenia PANSS score >40	Outpatients	Augmentation (FGA or SGA, fixed dose)	29 (15 EPA vs 14)	EPA 2000	12	+	NA	NA	+	NA	Moderate
Peet et al., 2001 (India)	India	Chronic schizophrenia PANSS score >40	Outpatients	Augmentation (FGA or SGA, fixed dose)	30 (16 DHA vs 14)	DHA 2000	12	ns	NA	NA	ns	NA	High
Emsley et al., 2002	**South Africa**	**Chronic schizophrenia PANSS score>50**	**Outpatients**	**Augmentation (FGA or SGA, fixed dose)**	**39 (19 vs 20)**	**EPA 3000**	**12**	**ns**	**ns**	**+**	**+**	**NA**	**Low**
Peet et al., 2002	**United Kingdom**	**Chronic schizophrenia PANSS score>50 Illness duration<20years**	**Outpatients**	**Augmentation (FGA or SGA, fixed dose)**	**57 (29 vs 28)**	**EPA 1000**	**12**	**ns**	**ns**	**ns**	**ns**	**NA**	**Low**
					52(24 vs 28)	**EPA 2000**	**12**	**ns**	**ns**	**ns**	**ns**	**NA**	**Low**
					53 (25 vs 28)	**EPA 4000**	**12**	**ns**	**ns**	**ns**	**ns**	**NA**	**Low**
Emsley et al., 2006	**South Africa**	**Chronic schizophrenia with tardive dyskinesia**	**Outpatients**	**Augmentation (FGA, fixed doses)**	**77 (39 vs 38)**	**EPA 2000**	**12**	**NA**	**NA**	**NA**	**ns**	**NA**	**Low**
Bošković et al., 2016	Slovenia	Chronic schizophrenia (illness duration≥3 years)	Outpatients	Augmentation (Haloperidol, flexible dose)	20 (9 vs 11)	EPA 396/ DHA 264	16	ns	ns	ns	ns	NA	High
Acute phase													
Pawelczyk et al., 2016	**Poland**	**First episode**	**Inpatients**	**Coinitiation (sulpiride or SGA, flexible dose)**	**71 (36 vs 35)**	**EPA 1320/ DHA 880**	**26**	**ns**	**ns**	**+**	**+**	**NA**	**Low**

Berger et al., 2007	Australia	First episode At least one psychotic symptom daily for more than 1 week (delusions, hallucinations, disorder of thinking and/or speech other than simple acceleration or retardation, and disorganized, bizarre, or markedly inappropriate behavior).	In and outpatients	Coinitiation (SGA, flexible dose)	69 (35 vs 34)	EPA2000	12	ns	ns	ns	ns	NA	Moderate
Robinson et al., 2019, Szeszko et al., 2021	USA	Early schizophrenia (n=46) or bipolar I with psychosis (n=4); (treated <2years) Current BPRS positive symptoms rated ≥4 (moderate) on one or more of: conceptual disorganization, grandiosity, hallucinatory behavior, unusual thought content	Inpatients	Coinitiation (risperidone, flexible dose)	24 (12 vs 12)	EPA 740/ DHA 400	16	ns	ns	+ (depression-anxiety)	ns	+/ns	Moderate
Bentsen et al., 2013	**Norway**	**Chronic schizophrenia**	**Inpatients**	**Coinitiation (FGA or SGA<3 weeks, flexible doses)**	**74(36 vs 38)**	**EPA 2000**	**16**	**+ (low PUFA)**	**ns**	**ns**	**+ (low PUFA)**	**NA**	**Low**
Manteghiy et al., 2008	Iran	Chronic schizophrenia	Inpatients	Coinitiation (Risperidone flexible dose)	85 (42 vs 43)	EPA 1080/ DHA 720	6	ns	ns	ns	ns	NA	Moderate
Jamilian et al., 2014	Iran	Chronic schizophrenia PANSS score >60	Inpatients/Outpatients (Unspecified)	Coinitiation (olanzapine, risperidone or clozapine, flexible dose)	60 (30 vs 30)	EPA 1000	8	ns	ns	+	+	NA	High
Qiao et al., 2018	China	Chronic schizophrenia in the first two weeks after hospitalization PANSS score >50	Inpatients	Coinitiation (FGA or SGA, flexible dose)	50 (28 vs 22)	EPA 540/ DHA 360	12	NA	NA	NA	ns	NA	High

Estrogens. Nine RCTs (one with three arms), N total=677. N estrogens=383. N placebo=294													
Chronic schizophrenia													
Ko et al. 2006	**South Korea**	**-Acute or stabilized -Chronic schizophrenia, schizoaffective or schizophreniform disorder Childbearing aged women (mean aged 33 years for estrogen group)**	**Inpatients**	**Augmentation (SGA, fixed doses)**	**28 (14 vs 14)**	**0.625 mg (conjugated estrogen with 2.5 mg of medroxyprogesterone acetate) (per os)**	**8**	**NA**	**+**	**+**	**NA**	**+/-**	**Low**
Kulkarni et al. 2008	**Australia**	**-Acute or stabilized phase -Chronic schizophrenia, schizoaffective or schizophreniform disorder Childbearing aged women (mean age 33 years in both groups)**	**In- and outpatients**	**Augmentation (FGA or SGA, fixed doses unspecified)**	**87 (51 vs 36)**	**0.1 mg Transdermal Estradiol**	**4**	**+**	**ns**	**+**	**+**	**NA**	**Low**
Kulkarni et al. 2011	**Australia**	- Middle-aged men -Chronic schizophrenia, schizoaffective disorder and 8 patients with first episode -PANSS>60	In- and outpatients	Augmentation, SGA (fixed doses unspecified) + 7 on mood stabilizer	51 (25 vs 26)	2 mg Estradiol valerate (per os)	2	ns	ns	+	ns	NA	Moderate
Ghafari et al. 2013	Iran	Chronic schizophrenia (institutionalized) Childbearing aged women (mean age 34 years in both groups)	Inpatients	Augmentation (FGA or SGA, fixed/flexible dose unspecified)	32 (16 vs 16)	0.625 mg Conjugated Estrogens (per os)	4	+	+	+	+	NA	High
Kulkarni et al. 2014	**Australia**	**Chronic schizophrenia or schizoaffective disorder (PANSS>60) Childbearing aged women Aged 18-45 (mean 35 years)**	**In- and outpatients**	**Augmentation (FGA or SGA, fixed doses)**	**121(59 vs 62)**	**0.1 mg Transdermal Estradiol**	**8**	**+**	**ns**	**+**	**+**	**ns**	**Low**

					124 (62 vs 62)	**0.2 mg Transdermal Estradiol**	**8**	**+**	**ns**	**+**	**+**	**ns**	**Low**
Weiser et al. 2019	**Republic of Moldova**	**Premenopausal women aged 19-46 years (median age, 38 years; interquartile range, 34-42 years)**	**In-and outpatients**	**Augmentation (FGA or SGA, fixed doses)**	**188 (95 vs 93)**	**0.2 mg Transdermal Estradiol**	**8**	**+**	**+**	**+**	**+**	**ns**	**Low**
Acute phase													
Kulkarni et al, 2001	Australia	Chronic middle-aged schizophrenia or schizoaffective or schizophreniform disorder Childbearing aged women (mean age 33 years in the estrogen group)	Not specified	Coinitiation (risperidone, flexible dose)	24 (12 vs 12)	0.05 mg Transdermal Estradiol	4	ns	ns	ns	ns	NA	Moderate
					24 (12 vs 12)	0.1 mg Transdermal Estradiol	4	+	+	+	+	NA	Moderate
Akhondzadeh et al. 2003	**Iran**	**Untreated Chronic schizophrenia (PANSS>60) Childbearing aged women (mean age 32 years in the estrogen group)**	**Inpatients**	**Coinitiation (haloperidol 15 mg, fixed dose)**	**32 (16 vs 16)**	**0.05 mg Ethynyl Estradiol (per os)**	**8**	**+**	**+**	**+**	**+**	**NA**	**Low**
Louza et al. 2004	Brazil	Childbearing aged women with schizophrenia in active phase (mean age 34 years in the estrogen group)	Not specified	Augmentation (haloperidol, fixed doses)	40 (21 vs 19)	0.625 mg conjugated estrogen (per os)	4	ns	ns	ns	ns	NA	Moderate
Selective estrogen receptor modulator (SERM) (Raloxifene). 9 RCTs. N total=552. N raloxifene=275. N placebo=277													
Chronic schizophrenia													
Kulkarni et al 2010	Australia	SZ, schizoaffective or schizophreniform disorder (PANSS>60) Peri or postmenopausal women	Not specified	Augmentation FGA or SGA (flexible doses unspecified)	26 (13 vs 13)	120	12	+	ns	+	ns	NA	Moderate

Usall et al. 2011	**Spain**	**SZ Postmenopausal women with at least one item score > 4 on the PANSS negative factor Stable dose of antipsychotics in the month before inclusion**	**In- (non acute) and outpatients**	**Augmentation (FGA or SGA, fixed doses)**	**32 (15 vs 17)**	**60**	**12**	**+**	**+**	**+**	**+**	**NA**	**Low**
Weickert et al, 2015	**Australia**	**Chronic SZ or schizoaffective disorders (both sexes) (mean PANSS ~60+/-18)**	**Outpatients**	**Augmentation (FGA or SGA flexible doses unspecified)**	**79 (40 vs 39)**	**120**	**6 (parallel) 13 (cross-over)**	**ns**	**ns**	**ns**	**NA**	**+ / ns**	**Low**
Kulkarni et al. 2016 Gurvich et al. 2019	**Australia**	**SZ or schizoaffective peri or post-menopausal middle-aged Women PANSS > 60 Stable dose of antipsychotics for at least 4 months**	**In and outpatients**	**Augmentation (FGA or SGA, fixed doses)**	**56 (26 vs 30)**	**120 120**	**12 12**	**ns NA**	**ns NA**	**+ NA**	**+ NA**	**ns ns**	**Low**
Usall et al. 2016 Huerta-Ramos et al. 2020	Spain	SZ Post-menopausal middle-aged women Chronic SZ with significant negative symptoms (at least one negative symptom score > 4 on the PANSS)	In- and outpatients	Augmentation (FGA or SGA, fixed doses)	57 (27 vs 30) 58 (31 vs 27)	60 60	24 24	ns NA	+ NA	+ NA	+ NA	NA ns	Moderate
Weiser et al. 2017	**Romania and Republic of Moldova**	**SZ Post-menopausal women CGI score≥4 OR score >= 4 on 2 of these PANSS items: delusions, hallucinations, conceptual disorganization, suspicion/persecution OR PANSS negative score >= 18 Antipsychotics for at least 2 weeks**	**In- and outpatients (13/187)**	**Augmentation (FGA or SGA, flexible doses unspecified)**	**174 (90 vs 84)**	**120**	**16**	**-**	**-**	**-**	**-**	**ns**	**Low**
Vahdani et al. 2020	**Iran**	**SZ Both genders**	**Not specified**	**Augmentation (FGA or SGA, fixed doses)**	**40 (20 vs 20)**	**60**	**6**	**NA**	**NA**	**NA**	**NA**	**+ / ns**	**Low**
Acute phase													

Kianimehr et al. 2014	Iran	SZ Post-menopausal women Duration of illness > 2 years PANSS > 60	Inpatients	Coinitiation (Risperidone 6 mg/day, fixed dose)	46 (23 vs 23)	120	8	+	ns	ns	ns	NA	Moderate
Khodaie-Ardakani et al. 2015	**Iran**	**SZ Men aged between 18-55 Duration of illness > 2 years PANSS > 60 Patients with depression excluded**	**Outpatients**	**Coinitiation (Risperidone 6 mg/day, fixed dose)**	**42 (21 vs 21)**	**120**	**8**	**ns**	**+**	**+**	**+**	**NA**	**Low**
Aspirin. Four RCTs. N total=424. N aspirin=221. N placebo=203													
Mix early-phase + chronic schizophrenia													
Laan et al. 2010	Netherlands	Schizophrenia or schizoaffective disorder <5 years (+26 patients <10 years), PANSS>60 with score 4 on 2 items, tested for 2 weeks observance before randomization	In and outpatients	Coinitiation (FGA+SGA, fixed dose)	58 (27 vs 31)	1000 (+pantoprazole 40mg)	12	+	ns	ns	+	ns	Moderate
Chronic schizophrenia													
Weiser et al. 2021	Romania (18 sites)/Republic of Moldova (one site)	Chronic schizophrenia or schizoaffective disorder with at least 2 psychotic episodes or continuous illness≥6months Score≥4 on at least one of the PANSS positive or disorganized items or ≥18 on PANSS negative factor	In- and outpatients	Augmentation (FGA + SGA for at least 2 weeks, flexible dose)	179 (91 vs 88)	1000 (+pantoprazole 40mg)	16	ns	ns	ns	ns	ns	Moderate
Weiser et al. 2021	Romania	Chronic schizophrenia or schizoaffective disorder with at least 2 psychotic episodes or continuous illness≥6months Score≥4 on two or more of the PANSS positive or disorganized items CRP>1mg/L	In- and outpatients	Augmentation (FGA + SGA for at least 2 weeks, flexible dose)	127 (63 vs 64)	1000 (+pantoprazole 40mg)	16	ns	ns	ns	ns	ns	Moderate
Acute phase													

Attari et al. 2017	Iran	Chronic schizophrenia (>2years)	In- and outpatients (unspecified)	Coinitiation (FGA + SGA, fixed dose)	40 (20 vs 20)	325 (+omeprazole 20mg)	6	+	+	+	+	NA	High
					40 (20 vs 20)	500 (+omeprazole 20mg)	6	+	+	+	+	NA	High
Celecoxib, Five RCTs. N total=440, N celecoxib=222, N placebo=218													
Chronic schizophrenia or early/chronic mix													
Rapaport et al. (2005)	USA	Chronic schizophrenia GAF<60	Outpatients	Augmentation (Olanzapine or risperidone, fixed dose unspecified)	35 (18 vs 17)	400	8	ns	ns	ns	ns	NA	Moderate
Acute phase													
Müller et al. (2010)	Germany	First episode schizophrenia	Inpatients	Coinitiation (Amisulpride, flexible dose)	37 (17 vs 20)	400	6	ns	+	ns	ns	NA	Moderate
Müller et al. (2002)	Germany	First episode and chronic schizophrenia	Inpatients	Coinitiation (Risperidone, flexible dose)	43 (21 vs 22)	400	5	ns	ns	ns	+	NA	Moderate
Rappard and Müller (2004)	USA	Chronic schizophrenia PANSS > 60	Inpatients	Coinitiation (Risperidone, flexible dose)	270 (138 vs 132)	400	11	ns	ns	ns	ns	NA	High
Akhondzadeh et al. (2007)	**Iran**	**Chronic schizophrenia PANSS > 60**	**Inpatients**	**Coinitiation (Risperidone, fixed dose 6mg/j)**	**55 (28 vs 27)**	**400**	**8**	**+**	**ns**	**+**	**+**	**NA**	**Low**

NA not available. Ns non-significant (p≥0.05). FGA first generation antipsychotics. SGA second-generation antipsychotics. PANSS Positive and Negative Syndrome Scale for Schizophrenia. RCT randomized controlled trials

Supplementary material 6. Detailed risk of bias analysis of the 63 randomized controlled trials (RCTs).

Study ID	Coinitiation or augmentation (antipsychotic treatment, flexible/fixed doses)	1.1 Focused question	1.2 Randomized assignment	1.3 Adequate concealment	1.4 Blindness	1.5 Similar groups at baseline	1.6 Only Treatment under investigation	1.7 Valid outcomes	1.8 Percentage of dropouts	1.9 Intention-to-treat analysis	1.10 All sites comparable	Risk of bias
NAC												
Conus et al. (2018)	Augmentation **(FGA + SGA, flexible dose)**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**3.2%**	Y	**DNA**	**Low**
Breier et al. (2018)	Augmentation (FGA + SGA, flexible dose)	**Y**	**Y**	Y	Y	Y	U	**Y**	46.7%	Y	**DNA**	Moderate
Davis et al. (2014)	Augmentation (FGA + SGA, unspecified flexible dose)	**Y**	**Y**	U	Y	U	U	**Y**	34.6%	Y	**DNA**	Moderate
Berk et al. (2008)	Augmentation (FGA + SGA, flexible dose)	**Y**	**Y**	Y	Y	Y	U	**Y**	40.0%	Y	**DNA**	Moderate
Rapado-Castro et al. (2017)	**Augmentation (FGA + SGA, flexible dose)**	**Y**	**Y**	**Y**	Y	Y	Y	Y	**U**	Y	**U**	**Moderate**
Sepehrmanesh et al. (2018)	**Augmentation (FGA + SGA + anti-cholinergic agents, fixed dose)**	**Y**	**Y**	**Y**	Y	N	Y	Y	**6.0%**	Y	**DNA**	**Low**
Zhang et al. (2015)	Coinitiation (risperidone)	**Y**	**Y**	U	U	U	U	**U**	U	U	**DNA**	High
Farokhnia et al. (2013)	**Coinitiation (risperidone flexible dose)**	**Y**	**Y**	**Y**	Y	Y	Y	Y	**8.7%**	Y	**DNA**	**Low**
Sarcosine												
Tsai et al. 2004	Augmentation (FGA + SGA, fixed dose, stable at least for 3 months, one patient untreated)	**Y**	**Y**	**Y**	**Y**	**N**	**Y**	**Y**	**5.2%**	**N**	**DNA**	High
Lane et al. 2010	Augmentation (SGA, fixed dose, stable at least for 3 months)	**Y**	**Y**	Y	Y	N	Y	**Y**	12.5%	N	**DNA**	Moderate

Lin et al. 2015	Augmentation (SGA, fixed dose, stable at least for 2 months)	**Y**	**Y**	Y	Y	Y	Y	**Y**	23.8%	N	**DNA**	Moderate
Strzelecki et al. 2015	Augmentation (FGA + SGA excluding clozapine, fixed dose, stable at least for 3 months)	**Y**	**U**	Y	Y	Y	Y	**Y**	U	U	**DNA**	Moderate
Lane et al. 2006	Augmentation (Clozapine, fixed dose, stable for at least 3 months)	**Y**	**N**	Y	Y	Y	Y	**Y**	O%	DNA	**DNA**	High
Lane et al. 2005	Coinitiation (Risperidone, flexible dose)	**Y**	**Y**	Y	Y	Y	Y	**Y**	13.7%	Y	**DNA**	Moderate
Minocycline												
Chaudhry et al. 2012	Augmentation (SGA+FGA unspecified, flexible dose unspecified)	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**33.3 %**	**Y**	**DNA**	Moderate
Liu et al. (2014)	**Augmentation (Risperidone, fixed dose)**	**Y**	**Y**	**Y**	Y	N	Y	Y	31.2 %	Y	**Y**	**Moderate**
Deakin et al. (2018)	**Augmentation (FGA and SGA, fixed dose)**	**Y**	**Y**	**Y**	Y	Y	Y	Y	**36.7 %**	Y	**DNA**	**Low**
Khodaie-Ardakani et al. (2014)	Augmentation (Risperidone, flexible dose)	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**5%**	**Y**	**DNA**	Low
Kelly et al. (2015)	**Augmentation (clozapine, fixed dose)**	**Y**	**Y**	**Y**	Y	Y	Y	Y	4%	Y	**U**	**Low**
Levkovitz et al. (2010)	Coinitiation (SGA including clozapine, flexible dose)	**Y**	**Y**	**U**	**U**	**Y**	**Y**	**Y**	**70%**	**Y**	**DNA**	High
Zhang et al. (2018) (3 arms)	Coinitiation (Risperidone,	**Y**	**Y**	Y	Y	Y	Y	**Y**	22% 26%	Y	**DNA**	Low

	flexible dose 3 to 6 mg)											
Weiser M. et al. (2019)	Augmentation (SGA+FGA unspecified, flexible dose unspecified)	**Y**	**Y**	Y	Y	Y	Y	**Y**	14.5 %	Y	**U**	Moderate
PUFAS												
Fenton et al., 2001	Augmentation (FGA or SGA, fixed dose)	**Y**	**U**	Y	Y	Y	Y	**Y**	16.7%	Y	**DNA**	Moderate
Peet et al., 2001 (UK)	Augmentation (FGA or SGA, fixed dose)	**Y**	**U**	U	Y	U	Y	**Y**	18.2%	N	**DNA**	Moderate
Peet et al., 2001 (India)	Augmentation (FGA or SGA, fixed dose)	**Y**	**U**	U	Y	U	N	**Y**	13.3%	N	**DNA**	High
Emsley et al., 2002	**Augmentation (FGA or SGA, fixed dose)**	**Y**	**Y**	**Y**	Y	Y	Y	Y	2.5%	Y	**DNA**	**Low**
Peet et al., 2002 (3 arms)	**Augmentation (FGA or SGA, fixed dose)**	**Y**	**Y**	**Y**	Y	Y	Y	Y	**7.8%**	Y	**U**	**Low**
Emsley et al., 2006	**Augmentation (FGA, fixed doses)**	**Y**	**Y**	**Y**	Y	Y	Y	Y	**8.3%**	Y	**DNA**	**Low**
Bošković et al., 2016	Augmentation (Haloperidol, flexible dose)	**Y**	**U**	**Y**	**Y**	**Y**	**Y**	**Y**	**14.7%**	**U**	**DNA**	High
Pawelczyk et al., 2016	**Coinitiation (sulpiride or SGA, flexible dose)**	**Y**	**Y**	**Y**	Y	Y	Y	Y	8.4%	Y	**DNA**	**Low**
Berger et al., 2007	Coinitiation (SGA, flexible dose)	**Y**	**Y**	**Y**	**Y**	**Y**	**N**	**Y**	**13.8%**	**Y**	**DNA**	Moderate
Robinson et al., 2019, Szeszko et al., 2021	Coinitiation (risperidone, flexible dose)	Y	Y	Y	Y	Y	Y	Y	30%	Y	DNA	Moderate
Bentsen et al., 2013	**Coinitiation (FGA or SGA<3 weeks, flexible doses)**	**Y**	**Y**	**Y**	Y	U	Y	Y	**25.7%**	Y	**U**	**Low**
Manteghiy et al., 2008	Coinitiation (Risperidone flexible dose)	**Y**	**Y**	**U**	**U**	**Y**	**U**	**Y**	**24.7%**	**N**	**DNA**	Moderate

Jamilian et al., 2014	Coinitiation (olanzapine, risperidone or clozapine, flexible dose)	**Y**	**U**	U	U	U	N	**Y**	U	N	**DNA**	High
Qiao et al., 2018	Coinitiation (FGA or SGA, flexible dose)	**Y**	**U**	U	U	Y	N	**Y**	48%	N	**DNA**	High
Estrogens												
Ko et al. 2006	**Augmentation (SGA, fixed doses)**	**Y**	**Y**	**Y**	Y	Y	Y	Y	0	Y	**DNA**	**Low**
Kulkarni et al. 2008	**Augmentation (FGA or SGA, fixed doses unspecified)**	**Y**	**Y**	**Y**	Y	Y	Y	Y	**14.7%**	U	**DNA**	**Low**
Kulkarni et al. 2011	Augmentation, SGA (**fixed doses unspecified**) + 7 on mood stabilizer	**Y**	**Y**	**U**	**Y**	**Y**	**Y**	**Y**	**3.8%**	**U**	**DNA**	Moderate
Ghafari et al. 2013	Augmentation (FGA or SGA, fixed/flexible dose unspecified)	**Y**	**Y**	U	Y	Y	Y	**Y**	0	Y	**DNA**	High
Kulkarni et al. 2014 (3 arms)	**Augmentation (FGA or SGA, fixed doses)**	**Y**	**Y**	**Y**	Y	Y	Y	Y	2.5%	Y	**DNA**	**Low**
Weiser et al. 2019	**Augmentation (FGA or SGA, fixed doses)**	**Y**	**Y**	**Y**	Y	Y	Y	Y	**6%**	Y	**DNA**	**Low**
Kulkarni et al, 2001 (3 arms)	Coinitiation (risperidone, flexible dose)	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**0**	**Y**	**DNA**	Moderate
Akhondzadeh et al. 2003	**Coinitiation (haloperidol 15 mg, fixed dose)**	**Y**	**Y**	**U**	Y	Y	Y	Y	0	Y	**DNA**	**Low**
Louza et al. 2004	**Augmentation (haloperidol, fixed doses)**	**Y**	**U**	**U**	U	Y	Y	Y	**0**	Y	**DNA**	**Moderate**
SERM												

Kulkarni et al 2010	Augmentation FGA or SGA (flexible doses unspecified)	**Y**	**Y**	Y	Y	Y	Y	**Y**	0 %	Y	**DNA**	Moderate
Usall et al. 2011	**Augmentation (FGA or SGA, fixed doses)**	**Y**	**Y**	**Y**	Y	Y	Y	Y	0 %	Y	**DNA**	**Low**
Weickert et al, 2015	**Augmentation (FGA or SGA flexible doses unspecified)**	**Y**	**Y**	**Y**	Y	Y	Y	Y	**23.6 %**	Y	**DNA**	**Low**
Kulkarni et al. 2016 Gurvich et al. 2019	**Augmentation (FGA or SGA, fixed doses)**	**Y**	**Y**	**Y**	Y	Y	Y	Y	**1.8 %** **U**	Y	**DNA**	**Low**
Usall et al. 2016 Huerta-Ramos et al. 2020	Augmentation (FGA or SGA, fixed doses)	**Y**	**Y**	**Y**	**Y**	**N**	**Y**	**Y**	**4.3 %** **14.7 %**	**Y**	**DNA**	Moderate
Weiser et al. 2017	**Augmentation (FGA or SGA, flexible doses unspecified)**	**Y**	**Y**	**Y**	Y	Y	Y	Y	14.5%	Y	**DNA**	**Low**
Vahdani et al. 2020	Augmentation (FGA or SGA, fixed doses)	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**9.1 %**	**U**	**DNA**	Low
Kianimehr et al. 2014	Coinitiation (Risperidone 6 mg/day, fixed dose)	**Y**	**Y**	U	Y	Y	Y	**Y**	U	U	**N**	Moderate
Khodaie-Ardakani et al. 2015	**Coinitiation (Risperidone 6 mg/day, fixed dose)**	**Y**	**Y**	**Y**	Y	Y	Y	Y	8.7 %	Y	**DNA**	**Low**
Aspirin												
Laan et al. 2010	Coinitiation (FGA+SGA, fixed dose)	**Y**	**Y**	**Y**	**Y**	**N**	**Y**	**Y**	**17.1 %**	**Y**	**Y**	Moderate
Weiser et al. 2021	Augmentation (FGA + SGA for at least 2 weeks, flexible dose)	**Y**	**Y**	Y	Y	N	Y	**Y**	10.5%	Y	**DNA**	Moderate
Weiser et al. 2021	Augmentation (FGA + SGA for at least 2 weeks, flexible dose)	**Y**	**Y**	Y	Y	N	Y	Y	20.6%	Y	**DNA**	Moderate

Attari et al. 2017	Coinitiation (FGA + SGA, fixed dose)	**Y**	**Y**	Y	Y	Y	U	Y	0 %	Y	**DNA**	High
Celecoxib												
Rapaport et al. (2005)	Augmentation (Olanzapine or risperidone, fixed dose unspecified)	**Y**	**Y**	**Y**	**Y**	**N**	**Y**	Y	**8.0 %**	**N**	**DNA**	Moderate
Müller et al. (2010)	Coinitiation (Amisulpride, flexible dose)	**Y**	**Y**	Y	Y	N	Y	Y	26.0 %	Y	**DNA**	Moderate
Müller et al. (2002)	Coinitiation (Risperidone, flexible dose)	**Y**	**Y**	Y	Y	U	Y	Y	14 %	Y	**DNA**	Moderate
Rappard and Müller (2004)	Coinitiation (Risperidone, flexible dose)	**Y**	**Y**	U	Y	U	Y	Y	U	U	**DNA**	High
Akhondzadeh et al. (2007)	**Coinitiation (Risperidone, fixed dose 6mg/j)**	**Y**	**Y**	**Y**	Y	Y	Y	Y	8.3 %	Y	**DNA**	**Low**

Y: Yes N:No U: Unclear (can't say) DNA does not apply. NA not available. Ns non-significant (p≥0.05). FGA first generation antipsychotics. SGA second-generation antipsychotics. PANSS Positive and Negative Syndrome Scale for Schizophrenia. RCT randomized controlled trials.

Supplementary material 7. Results supporting the recommendations: from Level of Evidence to WFSBP-grade recommendations.

Level of evidence (LoE)	WFSBP-grade
• "A": attributed in case of at least two RCTs with low risk of bias showing effectiveness AND absence of RCT with low risk of bias reporting non-significant effects. In case of conflicting results, the choice between A and B was guided by the presence of meta-analyses with low risk of bias concluding to effectiveness (A) or non-significant results (B). We have opted to use the term "provisional strong" instead of "strong" to qualify our recommendations, considering the limited number of studies available, in particular with low risk of bias. This choice acknowledges the possibility of future changes to these recommendations based on additional randomized controlled trials (RCTs). • B ("limited"): attributed in case of downgrading of LoE A or if at least one RCT with moderate risk of bias reported effectiveness, with absence of RCT with moderate risk of bias reporting non-significant results. • C ("weak"): attributed in case of at least one RCT with high risk of bias reporting effectiveness and absence of RCT with high risk of bias reporting non-significant results.	• WFSBP-grade 1 strong provisional recommendation in favor of treatment ('A' LoE and GOOD acceptability), • WFSBP-grade 2 limited provisional recommendation in favor of treatment ('A' LoE and MODERATE acceptability OR 'B' LoE and GOOD acceptability), • WFSBP-grade 3 weak provisional recommendation ('A' LoE and POOR acceptability OR 'B' LoE and MODERATE/POOR acceptability OR 'C' LoE and GOOD/MODERATE/POOR acceptability). • WFSBP-grade -1/-2/-3 strong/limited/weak provisional recommendations against treatment.
The two or three leading authors assessed independently the risk of bias of each RCT in three modalities ("low/moderate/high risk of bias"). All risks of bias were reviewed for the final validation by FB and GF. The year of publication was taken into account in case of missing information to assess the risk of bias, given that the standards for high-	

quality methodological reports evolved with time. Similarly, if the RCT was published as a brief report/short communication, this was taken into account if some information was missing and the general quality of the trial was evaluated as recommended in the SIGN methodology[8]. We also took into consideration the potential conflicts of interest reported by the authors to modulate the final risk of bias. The risk of bias was downgraded if the majority of studies concluding to effectiveness also reported potential conflicts of interest. The separation of levels of evidence and grades of recommendation is needed to allow to define first, second, third, etc. lines of treatment based on the quality of the source data, risk-benefit evaluation and other criteria for grading recommendations[9].		
Summary of the evidence	**Dose and duration / Study population**	**WFSBP-grade recommendations**
N-acetylcysteine		
Eight meta-analyses published between 2012 and 2020 explored the effectiveness of adjunctive NAC in schizophrenia [11–18]. Four were rated as high quality [12–14,16], including up to seven RCTs [13,16]. No additional RCT was retrieved from the databases searches. The present recommendations are therefore based on seven RCTs published in eight papers [19–26]. Sample sizes ranged from 17 to 139 patients. These last four meta-analyses concluded NAC was effective in improving negative symptoms.	The NAC dose ranged from 600 to 3,600mg/day for 8 to 52 weeks. Four RCTs tested adjunctive NAC at 600 to 2000mg vs. placebo during 8 to 12 weeks [22,23,25,26]. Three further RCTs tested adjunctive NAC at 1200 to 3600mg vs. placebo during 24 to 52 weeks [19–21,24]. Three RCTs explored the effectiveness of NAC augmentation in patients with chronic schizophrenia [19,23–25], three in patients with early-phase psychosis [20,21,26] and one in a mixed population of early-phase and chronic patients with psychotic disorder [22]. Two RCTs explored the effectiveness of NAC co-	Due to its good acceptability and most of the evidence ranging between A and B levels of evidence (LoE), adjunctive NAC at 1,200 to 3,600mg/day for at least more than 12 weeks is provisionally recommended to improve negative symptoms and general psychopathology in schizophrenia (WFSBP-grade 1), with currently better evidence for chronic schizophrenia. Additionally, NAC augmentation may also improve positive symptoms and cognition in chronic schizophrenia with limited evidence (WFSBP-grade 2).

	initiation in addition to risperidone in the acute phase first-episode schizophrenia[26] and one in patients with acute phase chronic schizophrenia [23].	
Sarcosine		
Five meta-analyses [27–31] (including three to six RCTs) explored the effectiveness of adjunctive sarcosine in schizophrenia. All were considered of moderate quality, and all suggested the effectiveness of sarcosine on negative symptoms in non-resistant schizophrenia (i.e. added to non-clozapine antipsychotics), but not in resistant schizophrenia (i.e. added to clozapine). The literature search retrieved no additional RCT, and six RCTs with moderate or high risk of bias were included in the present recommendations [5,32–36]. The sample sizes ranged from 20 to 50 participants. The risk of bias due to potential conflicts of interest was considered as high, as all but one RCTs	The sarcosine dose of 2g/day was used in all RCTs, for six to 24 weeks. All RCTs were carried out in chronic schizophrenia and two of them in patients with predominant negative symptoms[5] or with primary deficit syndrome[33]. Four RCTs included inpatients[32–35], one outpatients[5] and one a mix of in and outpatients[36].	Sarcosine is an amino-acid with excellent acceptability. 2g/day sarcosine augmentation for at least 12-24 weeks may improve negative symptoms (WFSBP-grade 2) in non-resistant schizophrenia but not positive symptoms, general psychopathology or cognition (WFSBP-grade -3). Sarcosine 2g/day co-initiation with antipsychotics in the acute phase of chronic schizophrenia may improve negative symptoms and general psychopathology (WFSBP-grade 2). Sarcosine may not be effective in treatment-resistant schizophrenia (WFSBP-grade -2).

were carried out by the same team reporting potential conflicts of interest.		
Minocycline		
Nine meta-analyses including up to 13 RCTs were identified [13–15,17,37–41], of which four were considered of high quality[13,14,38,39]. All high-quality meta-analyses found significant improvement of negative symptoms with minocycline but non-significant results for positive symptoms. Conflicting results were obtained regarding general psychopathology. Of these 13 RCTs, only eight were included in the present recommendations, because the others were not available. Sample sizes ranged from 33 to 200 participants.	Minocycline doses ranged from 50 to 300mg/day (mostly 100-200mg/day) for 8 to 52 weeks. Four RCTs explored the effectiveness of minocycline augmentation in chronic schizophrenia[4,42–44], and four in early-phase schizophrenia[45–48]. Three RCTs explored the effectiveness of minocycline co-initiation in the acute phase of schizophrenia (one in early-phase schizophrenia) [47], and two in chronic schizophrenia [4,44]).	Among the two RCTs with low risk of bias exploring the effectiveness of minocycline 200mg/day augmentation for at least 12-16 weeks, one found effectiveness for negative symptoms and general psychopathology and one found non significant results (positive symptoms: WFSBP-grade -1, negative symptoms and general psychopathology : WFSBP-grade 2). One RCT with low risk of bias found non significant results for all symptoms dimensions for resistant schizophrenia (patients treated with clozapine) (WFSBP-Grade -2). The only RCT with low risk of bias exploring cognition found non-significant results (WFSBP-grade -2). Minocycline 200 mg/day co-initiation with antipsychotics may be effective for improving negative symptoms (WFSBP-grade 2). For minocycline, the largest trial in early-phase schizophrenia was negative, and future trials should focus on enriched populations with chances of responding to a medication based on the medication mechanism of action.
PUFA		

Eight meta-analyses published between 2006 and 2021 explored the effects of PUFAs on schizophrenia[13–15,38,49–52]. Five had a low risk of bias[13,14,38,50,52]. The meta-analysis with the highest number of included RCTs (N=14) [13] found a small but significant improvement in positive symptoms and general psychopathology and non-significant results for negative symptoms in the groups receiving adjunctive PUFAs compared to those receiving placebo. Adjunctive PUFA use was also associated with a significant improvement in triglyceride blood levels but not body mass index, fasting glucose, total cholesterol, low-density lipoprotein cholesterol, or C-reactive protein. These results were maintained after removing high-risk of bias studies and those with small sample sizes. Meta-regression analyses revealed no effect of age, illness duration, dosage of PUFAs, eicosapentaenoic acid (EPA) / docosahexaenoic (DHA) ratio and triglyceride levels on these outcomes. No additional RCT was retrieved from our searches, and the 14 RCTs were	Eight RCTs explored the effectiveness of 1,000-3,000 mg/day EPA alone [55,57,61–64,66,67] and the rest tested a combination of EPA (396-1,080mg/day) with DHA (264-880 mg/day). Only one RCT has tested delivery of DHA alone[62]. The trial durations ranged from 6 to 26 weeks. All RCTs were carried out in patients with chronic schizophrenia except two that were carried out in acute phase first-episode [60,67] and one in early-phase schizophrenia [58,59].	PUFAs augmentation in chronic schizophrenia has no significant effect on positive and negative symptoms (WFSBP-grade -1) and cognition (WFSBP-grade -2). However, PUFAs can improve general psychopathology (WFSBP-grade 1), which may correspond to symptoms of anxiety and/or depression associated with schizophrenia - but specific RCTs are needed to confirm this. In the acute phase of chronic schizophrenia, PUFAs co-initiation with antipsychotics has a non-significant effects on positive symptoms (WFSBP-grade -2) but may be effective when prescribed for at least 16 weeks in patients with low PUFA blood levels (with at least 2,000mg/day EPA) (WFSBP-grade 2). In first-episode schizophrenia, PUFAs co-initiation with antipsychotics may be effective for general psychopathology (WFSBP-grade 2) but not for positive and negative symptoms (WFSBP-grade -2). In early-phase schizophrenia, PUFAs co-initiation with antipsychotics for at least 16 weeks (with at least 740mg/day EPA and 400 mg/day DHA) may be effective for depression, anxiety, and cognition in patients with schizophrenia (WFSBP-grade 2).

included in the present recommendations [53–67]. Sample sizes ranged from 20 to 85 participants.		
Aspirin		
Seven meta-analyses[12–15,68–70] including two to four RCTs explored the effectiveness of adjunctive aspirin in schizophrenia. All but one [15] had a low risk of bias. The latest meta-analysis [70] was the only one to include four RCTs and concluded there was no significant effect of adjunctive aspirin on any symptom dimension, with low heterogeneity. Four RCTs were included in the recommendations[70–72]. There was no risk of bias due to a conflict of interest. The sample size ranged from 40 to 200 patients.	The aspirin doses ranged from 325 to 1,000 mg/day for 6 to 16 weeks, combined with omeprazole or pantoprazole to prevent gastro-intestinal side-effects. All studies included in and outpatients. The results of two RCTs were published in the same article[70], and one RCT had three arms, comparing 325 mg/day and 500 mg/day aspirin to placebo[72]. In addition, one RCT included patients with an illness duration<10 years [72], one patient in the acute phase with at least two years of illness duration [72], and two included patients with at least two psychotic episodes[70]. Notably, one RCT included patients with low-grade peripheral inflammation defined by a CRP blood level≥1mg/L[70].	Aspirin augmentation is not recommended for schizophrenia, neither for the psychotic symptomatology nor for cognition (WFSBP-grade -2). However, there is weak evidence for the efficacy of 325 to 500 mg/day aspirin on positive and negative symptoms, and on general psychopathology in co-initiation with antipsychotics (combined with omeprazole) and for six weeks (WFSBP-grade 3).

Celecoxib		
Seven meta-analyses [12–15,38,68,73], including three to eight RCTs explored the effect of celecoxib in schizophrenia. Five had a low risk of bias [12–14,38,68]. Five RCTs were included in our review [74–78]. One meta-analysis [73] included two studies written in Chinese [79,80] and one study report results based on similar data [75] that were not included. A potential risk of bias due to conflict of interest was identified in three RCTs [75,76,78]. Sample sizes ranged from 35 to 270. All meta-analyses highlighted substantial-to-high heterogeneity between studies and failed to show a significant improvement in patients treated with celecoxib compared to placebo.	The celecoxib dose was 400mg/day in all trials in addition to antipsychotics. The observation period lasted from five to 11 weeks. One study included only first-episode patients [75], three studies only chronic schizophrenia patients [74,77,78], and one study with both first-episode and chronic schizophrenia patients [76].	400mg/day celecoxib may improve positive symptoms and general psychopathology in co-initiation with risperidone in the acute phase of chronic schizophrenia (WFSBP-grade 2) but not negative symptoms (WFSBP-grade -2). Celecoxib augmentation in stabilized outpatients is also not recommended (WFSBP-grade -2). No data were available about celecoxib's effectiveness on cognition.
Estrogens		
Three meta-analyses specifically explored the effectiveness of estrogens in schizophrenia (without pooling estrogens with Selective Estrogen Receptor Modulators (SERM's)) [15,38,81], including up to seven RCTs[15,38] with one RCT having three treatment arms (two doses) [82]. Two were rated as having a low risk	Authors used either transdermal estradiol 0.05 g/day to 0.2 g/day[82,83,86], conjugated oral estrogens 0.625 mg/day[84,88,89], ethynyl estradiol 0.05 mg/day[90] or estradiol valerate 2g/day [87] vs. placebo. The trials duration ranged from two to eight weeks.	Eight-week estrogen supplementation has a good acceptability and no RCT reported serious adverse events or increased rate of dropout in the groups with active treatments compared to placebo. All RCTs that included females included premenopausal/childbearing aged women to prevent the risk of increased thromboembolism and cancer with estrogen substitution in post-menopausal women.

of bias [38,81], and all suggested the effectiveness of adjunctive estrogens in positive and negative symptoms in women with schizophrenia. Therefore, two additional RCTs (one with low risk of bias[83] and one with moderate risk of bias [84]) were added to the present recommendations for a total of nine RCTs (one with three arms). Five RCTs were carried out by the same Australian team [82,85–87]. Two studies compared three arms, i.e., with two doses of estrogens (co-initiation of 0.05 mg/day and 0.1 mg/day transdermal estradiol vs. placebo in acute phase schizophrenia [85] and augmentation by transdermal estradiol 0.1 mg/day and 0.2 mg/day)[82]. The sample sizes ranged from 24 to 200. Of note, the last RCT with a low risk of bias and high sample size reported that the effectiveness was almost entirely due to the sample of women aged ≥38 years[83].	All RCTs included patients with chronic schizophrenia except one with a small proportion of first-episode patients [87]. In addition, all RCTs were carried out in women of childbearing-age, except for one conducted in men [87].	Eight-week transdermal estradiol augmentation appears effective in improving positive symptoms and general psychopathology in childbearing-aged women with chronic schizophrenia with provisional evidence of effectiveness but uncertain evidence of safety (WFSBP-grade 2) and with only limited evidence for negative symptoms (WFSBP-grade 2). Estrogen supplementation may be more effective in women aged ≥38 years. The optimal recommended form and dose for effectiveness appears to be transdermal estradiol 0.2 mg/day. Altogether, data are lacking for longer treatment durations in terms of effectiveness and safety, especially given that the most worrisome adverse events like cancer may take many years to manifest. We therefore took the decision not to recommend them at the highest level. Eight weeks oral 0.05 mg/day ethynyl estradiol co-initiation with antipsychotics may improve all symptom dimensions of chronic schizophrenia in childbearing aged women inpatients (WFSBP-grade 2). Adjunctive oral estradiol valerate 2 mg/day may be effective for general psychopathology in men with limited evidence (WFSBP-grade 2), but this treatment has been tested for only two weeks in

		one RCT, and additional trials with longer duration are needed to determine the effectiveness and safety of estradiol valerate.
Selective Estrogen Receptor Modulators (SERMs)		
Six meta-analyses have explored the effectiveness of adjunctive raloxifene in schizophrenia [13–15,38,91–93]. Three meta-analyses were of high quality [13,14,91] and included five to eight RCTs [94–101]. The results of two RCTs were published in the same article [97]. Three studies that assessed cognitive outcomes were published since the publication of the last meta-analysis and were included in the present recommendations. Two studies were related to the same RCT, so the recommendations were based on 10 RCTs [94–104]. Sample sizes ranged between 35 and 200 participants. The overall risk of bias regarding conflict of interest was low. The only meta-analysis with a low risk of bias and analyzing raloxifene alone concluded that raloxifene was effective in improving positive and negative symptoms and general psychopathology [91].	Doses of raloxifene ranged from 60 to 120mg/day for six 6 to 24 weeks. All RCTs were carried out in patients with chronic schizophrenia. All but two RCTs [94,95] were carried out in clinically stabilized patients. All but three RCTs included peri- or post-menopausal women only (one included men only in the acute phase schizophrenia [94] and two both sexes [100,104]). All RCTs included in- and outpatients, except for one RCT that included only inpatients [95]; two did not report hospitalization status [97,104].	60-120 mg/day raloxifene augmentation cannot be currently recommended in peri or post-menopausal women with schizophrenia, especially for positive and negative symptoms and for cognitive functioning in chronic schizophrenia (WFSBP-grade -2). Indeed, despite a relatively good acceptability of SERM, among the five RCTs with a low risk of bias, one with the largest sample size (larger than the remaining four RCTs) reported a worsening of all symptom dimensions. 120 mg/day raloxifene co-initiation with antipsychotics may improve negative symptoms and general psychopathology in men with acute-phase schizophrenia (WFSBP-grade 2).

Supplementary material 8. Context/rationale for the efficacy of each molecule, RCTs' global conclusions and risk of bias and subgroup analyses

N-acetyl-cysteine (NAC)

NAC is a neuroprotective agent with antioxidative, anti-inflammatory and glutamatergic properties [105].

RCTs' global conclusions and risk of bias

Regarding NAC augmentation for negative symptoms and general psychopathology, one RCT with low risk of bias found significant improvement after 12 weeks of 1,200mg/day administration [25], vs. one with low risk of bias finding non-significant results after 26 weeks of 2,700 mg/day administration [21]. Three meta-analyses (one with low and two with moderate risk of bias) found significant results vs. one meta-analysis (with moderate risk of bias) finding non-significant result. (LoE A: "provisional")

Regarding NAC augmentation for positive symptoms, one RCT with low risk of bias [25]) found significant improvement vs. one with low risk of bias h finding non-significant results. One meta-analysis (with low risk of bias) showed significant improvement in positive symptoms. (LoE B: "limited")

Regarding cognition, two RCTs with low risk of bias [21,25] found some significant improvement vs. no RCT with low risk of bias finding non-significant results. Two meta-analyses concluded to significant improvement of working memory but results were not convergent for all cognitive tests. (LoE B: "limited")

Regarding NAC coinitiation for negative symptoms one RCT with low risk of bias [23] found a significant improvement vs. no RCT reported non-significant results (LoE B: "limited"). The same RCT found non-significant results for general psychopathology (LoE -B: "limited").

Subgroup analyses

NAC in early psychosis

No RCT with low risk of bias found significant improvement of any symptom dimension in early psychosis vs. one with low risk of bias finding non-significant results (26 weeks, 2,700 mg/day) [21]. (LoE -B: "limited")

Sarcosine

Sarcosine, also known as *N*-methylglycine, is an intermediate and byproduct in glycine synthesis and degradation and a non-selective glycine-reuptake inhibitor mediated by GlyT1. Sarcosine is rapidly degraded to glycine, which, in addition to its importance as a constituent of proteins, plays

a significant role in various physiological processes as a prime metabolic source of components of living cells such as glutathione, creatine, purines and serine [106].

RCTs' global conclusions and risk of bias

In patients with non-resistant schizophrenia, sarcosine 2g/day augmentation was associated with a significant improvement of positive, negative symptoms, general psychopathology and cognition in respectively zero, two, zero and one RCTs with moderate risk of bias. vs. respectively one, one, one and zero RCT finding non-significant results (positive symptoms: LoE -C: "weak", negative symptoms: LoE C: "weak", general psychopathology: LoE -C: "weak", cognition: LoE B: "limited").

Regarding cognition, one RCT with moderate risk of bias [35] found mixed results and one with high risk of bias [33] non-significant results.

In patients with treatment-resistant schizophrenia, sarcosine 2g/day augmentation was associated with non-significant results in all symptoms' dimensions in one RCT [36] with high risk of bias. No RCT reported significant improvement (LoE -C: "weak").

Sarcosine 2g/day coinitiation with antipsychotics in acute phase chronic schizophrenia was associated with significant improvement in negative symptoms and general psychopathology in one RCT [34] with moderate risk of bias. No RCT reported non-significant results (LoE B "limited").

Subgroup analyses

One 24-week long RCT with moderate risk of bias [5] reported significant improvement of negative symptoms in the group treated with sarcosine 2g/day. One 12-week long RCT [35] with moderate risk of bias reported non-significant results. (LoE B: "limited")

Minocycline

Minocycline is a second-generation tetracycline antibiotic with a good penetration into the brain and with anti-inflammatory anti-apoptotic and anti-oxidant actions, modulating glutamate and monoamine neurotransmission and also, possibly, modulating microbiota composition [107].

RCTs' global conclusions and risk of bias

Regarding minocycline augmentation, one RCT with low risk of bias found a significant improvement of negative symptoms (but not positive symptoms, general psychopathology and cognition) in chronic schizophrenia [42], vs. one RCT with low risk of bias finding non-significant results[48].

One RCT with low risk of bias found non-significant results for all symptoms' dimensions in patients with resistant schizophrenia treated with clozapine [43] (LoE -B: "limited").

Regarding cognition, one RCTs with low risk of bias [43] found non-significant results with minocycline 200 mg/day for 10 to 16 weeks (LoE -A: " provisional").

Regarding minocycline co-initiation in patients with acute phase chronic schizophrenia, one RCT with low risk of bias [4] with three arms (minocycline 100mg/day, 200 mg/day and placebo) found a significant improvement of negative symptoms in the minocycline 200mg/day arm but non-significant results in the other arms (minocycline 200mg/day: LoE B: ”limited”, minocycline 100mg/day: LoE -B: ”limited”) and non-significant results in all arms for positive symptoms and general psychopathology (LoE -B: “limited"). For cognition, one RCT with moderate risk of bias [44] found non-significant results (LoE -B: “limited").

Subgroup analyses

Regarding minocycline long-term augmentation (≥12 weeks) in early schizophrenia, one RCT with low risk of bias found non-significant results for all symptoms dimensions for minocycline 300 mg/day for 52 weeks [48] (LoE -B: “limited”). Regarding cognition, one RCT with moderate risk of bias [46] found non-significant results (LoE -B: “limited”).

PUFAs

Lower levels of PUFAs have been reported in the blood of people with schizophrenia compared to healthy volunteers [108]. PUFAs have anti-inflammatory properties and may be associated with cognitive impairment [109].

RCTs’ global conclusions and risk of bias

Six RCTs[61–66] explored the effectiveness of adjunctive PUFA augmentation in chronic patients with schizophrenia. One RCT with low risk of bias[64] reported a significant improvement of general psychopathology, while one other with low risk of bias found non-significant results [66] (LoE B: “limited”). Regarding positive and negative symptoms, the two RCTs with low risk of bias [64,66] found non-significant results (LoE -A: “provisional”). Regarding cognition, one RCT[63] with moderate risk of bias found non-significant results (LoE B: “limited”).

Seven RCTs explored the effectiveness of adjunctive PUFA coinitiation with antipsychotic treatments in acute phase of schizophrenia[54–60,67].

Regarding positive symptoms, one RCT with low risk of bias[57] showed significant improvement of positive symptoms on patients with low blood level of PUFA, while one RCT with low risk of bias [60] found non-significant results (but without measuring PUFA blood levels). One meta-analysis[13] with low risk of bias including the highest number of studies found a small but significant improvement of positive symptoms (patients with low PUFA blood level: LoE B “limited”).

Regarding negative symptoms, two RCTs with low risk of bias[57,60] found non-significant results. (LoE -A: “provisional”)

Regarding general psychopathology, one RCT[60] with low risk of bias found significant improvement vs. one with low risk of bias finding non-significant results[57]. One meta-analysis[13] with low risk of bias including the highest number of studies found a small but

significant improvement of general psychopathology (LoE B: "limited"). Regarding cognition, only one RCT with moderate risk of bias [59] found improvement in some tests but not in others (LoE B: "limited").

Subgroup analysis

Regarding illness course of schizophrenia, one RCT with low risk of bias [60] found a significant improvement of general psychopathology in first episode schizophrenia after 26 weeks of PUFA administration(LoE B: "limited"). No significant improvement was observed for positive and negative symptoms (LoE -B: "limited").

Regarding PUFAs and doses in RCT with low risk of bias and significant results, one RCT[60] found that patients treated with adjunctive EPA 1320 DHA 880 mg/day fish oil co-initiation for 26 weeks had a significant improvement on general psychopathology compared to those treated with placebo. In the second RCT[57], adjunctive EPA 2,000mg/day co-initiation was effective in improving positive symptoms of chronic schizophrenia only in patients with low PUFA level.

COX inhibitors (Aspirin, Celecoxib)

The inflammatory hypothesis for schizophrenia has been supported by evidence from basic science, epidemiological associations and biomarkers studies [110,111]. Cyclooxygenase (COX) inhibitors (including anti-COX-1 low-dose aspirin, anti-COX-2 celecoxib and anti-COX1/anti-COX2 high-dose aspirin) suppress the production of prostaglandins and thromboxanes involved in the inflammatory processes [112]. Aspirin also reduces the hypothalamic-pituitary-adrenal axis response [113]. In contrast to celecoxib which can easily cross the blood-brain barrier, aspirin levels in the central nervous system are lower than in peripheral blood [114]. They have been the most studied COX inhibitors in schizophrenia thus far.

Aspirin

RCTs' global conclusions and risk of bias

Three RCTs were classified with moderate risk of bias[70,71] and one with high risk of bias[72].

Two RCTs with moderate risk of bias reported no significant effect of aspirin augmentation in chronic schizophrenia[70] vs. one RCT with moderate risk of bias finding significant improvement of positive symptoms in the group treated with 1,000mg/day aspirin+pantoprazole and non-significant results for negative symptoms and general psychopathology)[71] (all symptoms dimensions LoE -B "limited").

One RCT with high risk of bias reported significant improvement of all symptoms dimensions in the two arms receiving aspirin 325mg/day and 500 mg/day combined with omeprazole [72] (LoE C "weak").

On the three studies exploring cognition, all reported non-significant effects of aspirin augmentation[70] or co-initiation[71].

Celecoxib

RCTs' global conclusions and risk of bias

One RCT with moderate risk of bias found non-significant results for celecoxib augmentation in chronic schizophrenia[77] (LoE -B "limited").

One RCT with low risk of bias found significant improvement of positive symptoms and general psychopathology in acute phase of chronic schizophrenia inpatients treated with a combination of risperidone 6mg/day + celecoxib compared to risperidone 6 mg/day + placebo, and non-significant results for negative symptoms [74] (positive symptoms and general psychopathology LoE B "limited", negative symptoms LoE -B "limited").

Subgroup analyses

One meta-analysis suggested that celecoxib might exhibit better results in patients with first episode schizophrenia [73] but the two related studies[75,76] had a moderate risk of bias and obtained contradictory results: improvement of negative symptoms in only one RCT [75], or of general psychopathology in the other RCT [76] (negative symptoms and general psychopathology LoE B "limited", positive symptoms LoE -B "limited").

Estrogens and Selective Estrogen Receptor Modulators (SERM)

Steroid hormones modulate neurotransmitter system, neuroplasticity, memory and learning, innate immune signaling pathways and inflammatory mediators with sex differences.

Estrogens

RCTs' global conclusions and risk of bias

Transdermal estradiol 0.1 to 0.2mg/day augmentation was associated with significant improvement of positive symptoms and general psychopathology of chronic stabilized schizophrenia in women of child-bearing age in three RCTs with low risk of bias (one with three arms reporting similar effects in the two active arms)[82,83,86], with no RCT with low risk of bias finding non-significant results. (LoE A: "provisional")

Transdermal estradiol 0.2mg/day augmentation was associated with significant improvement of negative symptoms of chronic stabilized schizophrenia in women in one RCT with low risk of bias [83] vs. non-significant results in two RCTs with low risk of bias carried out by the same team (two with 0.1mg/day and one arm with 0.2mg/day)[82,86]. The meta-analyses reported significant improvement of negative symptoms (LoE B: "limited")

Oral 0.625 mg conjugated estrogen with 2.5 mg of medroxyprogesterone acetate was associated with significant improvement of negative symptoms of chronic stabilized schizophrenia in women of child-bearing age in one RCT with low risk of bias[88] with no RCT with low risk of bias reporting non-significant results. (LoE B: "limited")

Oral 0.05 mg ethynyl estradiol co-initiation with antipsychotics has shown significant improvement in all symptom dimensions of chronic schizophrenia in one RCT with low risk of bias including childbearing aged female inpatients [90]. (LoE B: "limited")

Oral 0.625 mg conjugated estrogen co-initiation with antipsychotics has shown non-significant results in all symptom dimensions of chronic schizophrenia in one RCT with moderate risk of bias including childbearing aged women [84]. (LoE -B: "limited")

Adjunctive oral estradiol valerate 2mg/day for two weeks was associated with significant improvement of general psychopathology in men in one RCT with moderate risk of bias [87] (LoE B: "limited"). Of note, no feminization side effects were reported in this RCT probably due to the short duration of treatment.

SERM

RCTs' global conclusions and risk of bias

Raloxifene 60-120 mg/day augmentation was associated with contradictory results on symptoms of schizophrenia, in five RCTs with low risk of bias [96,98–101].

Regarding cognition, two RCTs with low risk of bias found a significant improvement in some tests but not in others [100] [104]. Both RCTs included both men and women. Two other RCTs including only peri- or post-menopausal women (and published in three papers) found non-significant results [96,101,102] and one meta-analysis with low risk of bias [115]found non significant results on cognition (LoE B "limited").

In men, raloxifene 120 mg/day coinitiation with antipsychotics was associated with significant improvement in negative symptoms and general psychopathology (LoE B: "limited") (but not in positive symptoms) with acute phase schizophrenia in one RCT with low risk of bias [94].

In post-menopausal women, raloxifene 120 mg/day coinitiation with antipsychotics was associated with significant improvement in positive symptoms in one RCT with moderate risk of bias [95] (LoE B: "limited").

Subgroup analyses

Concerning long-term administration, in one RCT with moderate risk of bias lasting 24 weeks [98,103], adjunctive 60 mg/day raloxifene was associated with significant improvement of negative symptoms and general psychopathology (LoE B: "limited") but not positive symptoms and cognition (LoE -B: "limited").

Three RCTs with low risk of bias included only peri or post-menopausal women [96,99,101,102], raloxifene 60-120mg/day augmentation was associated with contradictory results. Regarding negative symptoms, one RCT (n=32) showed a significant improvement [99], one (n=69) showed

non-significant results [96], and one (n=174) showed significant worsening [101] (LoE -B: "limited"). Regarding general psychopathology, two RCTs showed a significant improvement [99] [96], and one (n=174) showed significant worsening [101] (LoE B: "limited").

No RCT included childbearing-age women (LoE 4 "lack of evidence").

Supplementary material 9. Complementary analyses on sample size, risk of bias and country economic status

Previous meta-analyses (including respectively 56 and 70 RCTs) have reported that effect sizes were inversely correlated with sample size [13,14]. This means that studies with a larger sample size have a lower propensity to show significant improvements. Regarding our 63 RCTs, we performed complementary analyses for each symptom dimension and cognition to estimate whether or not the probability of observing a significant improvement was influenced by sample size. Importantly, the analysis was not performed on standardized mean difference but on the presence/absence of any significant effect as this was used to formulate our recommendations. Similarly, we have checked a possible influence of the level of risk of bias.

To investigate the putative influence of sample size or risk of bias on our results, we performed a series of logistic regression analyses in which the presence(1)/absence(0) of a significant improvement of positive symptoms, negative symptoms, general psychopathology, cognition was entered as dependent variables. The total sample size and the risk of bias (low vs. medium vs. high) were entered successively as predictors.

(model 1) Improv(1/0) = cons + *a* x Samplesize

(model 2) Improv(1/0) = cons + *b* x Riskofbias

(model 3) Improv(1/0) = cons + *a* x Samplesize + *b* x Riskofbias

All analyses were performed under a Bayesian framework. For each symptom dimensions, we calculated:

1) the mean (*M*) and credible interval (CI95%) of the coefficient *a* and the probability that *a* was greater than 0

2) the ORs and credible intervals (CI95%) of medium/low, high/medium, high/low and the probability that each OR was greater than 1.

Probabilities were regarded as meaningful if they were either lower than 2.5% or higher than 97.5% [keeping in mind for instance that *Pr*(low>high)=1-*Pr*(high-low)].

A burn-in of 5,000 iterations followed by 100,000 iterations was used for each of the three chains, yielding a final 300,000 iteration sample for retrieving the characteristics of the posterior distribution. Convergence of the Markov chain Monte Carlo (MCMC) sample chains was checked graphically and was observed in each case. All computations were performed in the R computing environment with the required additional packages (in particular r2jags).

Results showed (see results in the table below):

- no meaningful influence of sample size for all symptom dimensions, except for cognition (in both models 1 and 3) in which larger sample sizes were associated with a lower probability of significant cognitive improvement
- a trend for a higher probability to find a significant improvement of positive symptoms and of cognition in studies with low compared to moderate risk of bias
- a higher probability to find a significant improvement of general symptomatology in studies with low compared to moderate risk of bias (in both models 2 and 3)

		Positive symptoms				Negative symptoms			
Model		*M*/OR	CI 95%		*Pr*	*M*/OR	CI 95%		*Pr*
1	sample size	0.136	[-0.428	0.684]	0.692	-0.188	[-0.778	0.349]	0.256
2	**medium vs. low**	**0.304**	[**0.075**	**1.115**]	**0.037**	0.699	[0.216	2.252]	0.273
	high vs. low	1.060	[0.200	5.391]	0.528	0.950	[0.179	4.803]	0.475
	high vs. medium	3.498	[0.637	19.93]	0.926	1.360	[0.267	6.652]	0.648
3	sample size	0.081	[-0.518	0.668]	0.612	-0.221	[-0.829	0.331]	0.226
	medium vs. low	**0.306**	[**0.074**	**1.138**]	**0.039**	0.654	[0.197	2.134]	0.243
	high vs. low	1.069	[0.195	5.638]	0.532	0.910	[0.168	4.728]	0.455
	high vs. medium	3.515	[0.617	20.56]	0.922	1.391	[0.267	7.098]	0.656

		General symptomatology				Cognition			
Model		*M*/OR	CI 95%		*Pr*	*M*/OR	CI 95%		*Pr*
1	**sample size**	-0.098	[-0.662	0.437]	0.366	**-1.758**	[**-3.67**	**-0.408**]	**0.002**
2	**medium vs. low**	**0.211**	**[0.057**	**0.709]**	**0.006**	0.373	[0.053	2.253]	0.141
	high vs. low	0.562	[0.100	3.122]	0.252	1.221	[0.029	50.90]	0.546
	high vs. medium	2.687	[0.481	15.32]	0.873	3.297	[0.075	150.8]	0.751
3	**sample size**	-0.199	[-0.818	0.379]	0.256	**-2.882**	[**-6.10**	**-0.780**]	**<0.001**
	medium vs. low	**0.195**	**[0.050**	**0.677]**	**0.005**	**0.101**	[**0.005**	**1.087**]	**0.030**
	high vs. low	0.521	[0.088	3.048]	0.231	0.071	[0.001	5.163]	0.107
	high vs. medium	2.683	[0.474	15.89]	0.868	0.731	[0.014	40.35]	0.433

Note: M=mean, OR=odds ratio, CI95%=credible interval 95%, Pr=probability that $a > 0$ or OR > 1 accordingly

In conclusion, we found no significant association between sample size and the probability of observing a significant improvement of positive symptoms, negative symptoms or general

symptomatology. However, a higher sample size was associated with a lower probability of observing significant cognitive improvement. Studies with a low risk of bias had a higher probability than studies with moderate risk of bias of showing a significant improvement in general symptomatology. A similar trend was observed for positive symptoms and cognition, but not for negative symptoms.

As some authors have suggested that results may vary between high and middle income countries[6], we conducted additional sensitivity analyses in which we examined whether the probability to find positive results was higher in upper middle vs. high income countries.
Upper middle income countries were: China, India, Iran, Romania/Moldavia, South Africa; high income countries were: Australia, Norway, Poland, Spain, South Korea, Switzerland, UK, USA[7].
First of all, the proportion of low, moderate, and high risk of bias studies was similar between upper middle-income and high-income countries (Chi2 = 4.2, p = 0.121).
Second, the probability of finding a positive (significant) result was higher in upper middle-income studies compared to high-income studies for negative symptoms (Pr = 0.992), but not for positive symptoms (Pr = 0.878) and general symptomatology (Pr = 0.870), regardless of the risk of bias. Similar results were obtained when we restricted our analyses to low-risk-of-bias studies. The probability of finding a positive (significant) result was higher in upper middle-income countries compared to high-income countries for negative symptoms (Pr > 0.999), not for positive symptoms (Pr = 0.744), but showed a trend for general symptomatology (Pr = 0.965).
When considering only the studies related to NAC, estrogens, and PUFAs (the drugs that have shown the best level of evidence for efficacy), similar results were obtained. However, these results should be interpreted with caution as the number of studies considered here was quite low (between three and five).
These analyses thus provide some arguments to question a possible bias associated with the country where the study was conducted.

		Risk of bias			
Country	Number of studies	Low	Moderate	High	Total
High	Total	12 (36.4%)	21 (54.6%)	5 (9.1%)	38 (100%)
	With significant results				
	Pos (%)	4 (33.3%)	4 (22.2%)	1 (0%)	9 (24.2%)
	Neg (%)	1 (8.3%)	8 (33.3%)	1 (0%)	10 (21.2%)
	Gen (%)	5 (41.7%)	7 (0%)	1 (0%)	13 (15.2%)
Upper middle	Total	13 (41.9%)	8 (35.5%)	6 (22.6%)	27 (100%)
	With significant results				
	Pos (%)	6 (30.7%)	1 (9.1%)	3 (0%)	10 (16.1%)
	Neg (%)	10 (61.5%)	2 (36.4%)	3 (57.1%)	15 (51.6%)
	Gen (%)	10 (61.5%)	0 (9.1%)	3 (57.1%)	13 (41.9%)
Total	Total	25 (39.1%)	29 (45.3%)	11 (15.6%)	65 (100%)
	With significant results				
	Pos (%)	10 (32.0%)	5 (27.6%)	4 (0%)	13 (20.3%)
	Neg (%)	11 (36.0%)	10 (31.0%)	4 (40.0%)	23 (35.9%)
	Gen (%)	15 (52.0%)	7 (44.8%)	4 (40.0%)	18 (28.1%)

Significant results = positive significant results; % = proportion of studies with positive significant results. The number of studies slightly differ from that reported in Table 1, as double arm studies were rated twice in case of discrepant results between arms. Also, Peet et al. 2001 study[62] was conducted both in UK and in India and was thus reported twice.

Details of the studies with low risk of bias

Agent	High income countries (k=12) Australia, Norway, Poland, South Korea, Spain, Switzerland, UK, USA	Upper middle income countries (k=12) Iran, Romania, South Africa, China
NAC	*Augmentation* Conus et al., 2018 (ns/ns/ns) early schizophrenia	*Augmentation* Sepehrmanesh et al., 2018 (+/+/+) chronic schizophrenia *Co-initiation* Farokhnia et al., 2013 (ns/+/ns) acute schizophrenia
PUFA	*Augmentation* Peet et al., 2002 (ns/ns/ns) Pawelczyk et al., 2016 (ns/ns/+) Bentsen et al., 2013 (+/ns/ns)	*Augmentation* Emsley et al., 2002 (ns/ns/+) Emsley et al., 2006 (ns)
Estrogens	*Augmentation* Ko et al., 2006 (NA/+/+) Kulkarni et al., 2008 (+/ns/+) Kulkarni et al., 2014 (+/ns/+)	*Augmentation* Weiser et al., 2019 (+/+/+) *Co-initiation* Akhondzadeh et al., 2003 (+/+/+)
Minocycline	*Augmentation* Deakin et al., 2018 (ns/ns/ns) Kelly et al., 2015 (ns/ns/ns)	*Augmentation* Khodaie-Ardakani et al., 2014 (ns/+/+) *Co-initiation* Zhang et al. (2018)) (ns/+,ns/ns)
SERM	*Augmentation* Usall et al., 2011 (+/+/+) Weickert et al, 2015 (ns/ns/ns) Kulkarni et al. 2016 (ns/ns/+)	*Augmentation* Weiser et al., 2017 (-/-/-) Vahdani et al., 2020 (+,ns for cognition) *Co-initiation* Khodaie-Ardakani et al., 2015 (ns/+/+)
Celecoxib		Akhondzadeh et al., 2007

Note: (positive/negative/general psychopathology). + = positive significant result; ns = non significant result; - negative significant result.

Supplementary material 10. References for supplementary material

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