



Anti-inflammatory medications for the treatment of mental disorders: A scoping review[☆]

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ABSTRACT

This scoping review assessed the effect of anti-inflammatory medications in mental disorders. A search in Medline and the Cochrane database focusing on randomised controlled trials and systematic reviews identified 53 primary research articles, conducted in major depression, bipolar disorder, schizophrenia and somatic symptom disorders and related disorders (SSRD).

The findings suggest that there is scope to consider the use of anti-inflammatory agents in mental disorders, however, not as a one-size-fits-all solution. Treatment could be especially helpful in subgroups with evidence of baseline inflammation. Anti-inflammatory medications that seem mostly effective in bipolar disorder or major depressive disorder, such as Celecoxib, Pioglitazone and statins, may differ from the ones with indications of effectiveness in schizophrenia, such as Minocycline and Aspirin. This might suggest a different underlying mechanism for treatment success in those two main illness groups. Further studies with larger sample sizes are needed that take levels of inflammation markers into account.

1. Background

There is a growing body of evidence to support the role of low-grade inflammation in the pathogenesis of mental disorders. The so called “sickness behaviour” induced by pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF α) includes symptoms such as malaise, fatigue, anorexia, cognitive problems and pain (Dantzer, 2009), which, if sustained, align with symptoms of mental disorders. This includes somatic symptom disorders and related disorders (SSRD) that concern physical symptoms that give rise to significant emotional, cognitive and behavioural distress to such an extent that daily functioning is impaired.

Peripheral markers of inflammation such as IL-6, TNF α and CRP (Strawbridge et al., 2015; Howren et al., 2009; Haapakoski et al., 2015;

Goldsmith et al., 2016) are found to be elevated in depressed patients versus healthy controls. IL-6 decreased with antidepressant treatment whilst treatment failure was associated with persistently high TNF α (Strawbridge et al., 2015). Cytokine inhibitors used in the treatment of chronic inflammatory disorders improved depressive symptoms as a secondary outcome measure, irrespective of the improvement in the primary physical illness (Kappelman et al., 2018). Elevated levels of proinflammatory cytokines such as IL-6, IL-8, TNF α and INF- γ (Miller et al., 2011; Frydecka et al., 2018; Mondelli et al., 2015) and reduced levels of anti-inflammatory cytokines such as IL-10 (Frydecka et al., 2018) have also been demonstrated in psychotic disorders and correlated with symptom severity as well as a poor response to antipsychotics (Mondelli et al., 2015; Enache et al., 2021; Kose et al., 2021).

Systemic Low-grade Inflammation (SLI) might have a potential role

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in functional neurological disorder (FND) and other SSRDs, given the significant association these conditions have with early life trauma and stressful life events, as well as the overlap with other comorbid mental disorders (O'Connell et al., 2020). Indeed, elevated levels of high sensitivity CRP and IL-6 were found in patients with SSRD, which was associated with increasing somatic symptoms and pain scores (van der Feltz-Cornelis et al., 2020). Elevated levels of cytokines including IL-6, IL12, IL17 and TNF α as well as microRNAs involved in inflammation, but significantly lower VEGFa and normal IL1b were found in patients with functional neurological disorder (FND) (van der Feltz-Cornelis et al., 2021). Another study of heterogeneous medically unexplained symptoms found a significant elevation in natural killer cells and B lymphocyte levels which are associated with inflammation (Houtveen et al., 2007).

These findings suggest that anti-inflammatory treatment might be helpful in treatment of mental disorders and indeed there are now a growing number of trials examining their effect. A review conducted in 2014 (Fond et al., 2014) considered the use of anti-inflammatory treatments as add-on treatments across mental disorders. Given the number of studies which have been published in this area since then, it was considered important to undertake this review and to collate the evidence for anti-inflammatory medication of all classes across all mental disorders to inform future research.

1.1. Aim

The aim of this review was to evaluate the effect of anti-inflammatory medications in the treatment of mental disorders including somatic symptom related disorders (SSRDs).

2. Methods

A scoping review (Munn et al., 2018) was conducted to identify evidence in the research literature of anti-inflammatory medications being used for anti-inflammatory purposes to treat people with mental disorders (Peters et al., 2015, 2020).

2.1. Search strategy

Searches were conducted in Medline and Cochrane databases up to July 2022. A complete list of search terms is included in Appendix 1. As hand searching, systematic reviews were used to identify primary research studies from their references that were not included in the randomised controlled trials search and additional relevant papers were found separately. Searches were limited to studies involving humans; no date or language limits were applied.

2.2. Study selection

This review focused on randomised controlled trials (RCTs) and systematic reviews (SRs) published between 1946 and July 15, 2022 in Medline, and between 1995 and July 15, 2022 in Cochrane databases.

Search results were uploaded to Rayyan software (Ouzzani et al., 2016). Duplicate studies were identified and removed. Titles and abstracts were screened against the pre-defined inclusion and exclusion criteria presented in Table 1 by three reviewers (JS, WHC and RF).

This process was piloted with dual screening completed for the initial 10% to establish reliability before reviewers completed independent screening of the remaining titles and abstracts. Screening agreement of 91–92.7% was achieved (Cohen's Kappa ranged between 0.53 and 0.75) (McHugh, 2012) for the first 10% of references. After that, titles, abstracts and full text were divided and screened by JS, RF and WHC and discrepancies and uncertainties were resolved through discussion or consultation with a fourth reviewer (CFC).

Table 1

Criteria for inclusion and exclusion.

Inclusion criteria	Exclusion criteria
Randomised controlled trials	Study protocols
Systematic reviews	All other study design types
Anti-inflammatory medications used for treatment	Medications associated with the development of mental disorders
Mental disorders or medically not yet explained physical health symptoms/SSRD	Alternative treatments
Adults (18 years and older)	Dietary supplements
Studies with a primary outcome assessing clinical improvement in mental health or medically not yet explained symptoms	Studies of participants under the age of 18 years

2.3. Data synthesis

We present the results in the Tables by psychiatric condition and grouped by medication type. In the discussion, we discuss the findings and explore their clinical and research relevance.

3. Results

Initial searches identified 3800 references for this review. Fig. 1 presents the full Prisma diagram showing references considered during the study selection process. Reviewers were not able to obtain full texts for 13 of the selected studies, that hence were excluded.

53 original articles reporting randomised controlled trials published between January 2002 and July 2022 were included in this review. 17 systematic reviews published between 2013 and 2021 were identified during searches (see Appendix 2). Six relevant primary research articles identified from systematic reviews were included in this review; these are shown as papers found through hand searching in Fig. 1.

The majority of references focused on depressive disorders and psychotic disorders; one considered SSRD (chronic fatigue syndrome). A range of medications were reported including non-steroidal anti-inflammatory drugs (Acetylsalicylic acid or Aspirin; Celecoxib), Minocycline, cytokine inhibitors (Anakinra; Infliximab; Tocilizumab; Adalimumab), Other (Atorvastatin; Hydroxychloroquine; Methotrexate; Pentoxifylline; Pioglitazone; Pravastatin; Prednisolone; Simvastatin). Sample sizes reported for primary studies ranged between 30 and 266 participants and included studies using a range of primary outcome measures (see Appendix 3). All studies were placebo-controlled. Data from included primary research studies are presented by condition and then by type of medication.

3.1. Mood disorders: bipolar affective disorder

3.1.1. Non-steroidal anti-inflammatory drugs

NSAIDs are competitive inhibitors of the cyclooxygenase enzyme, which converts arachidonic acid to thromboxane, prostaglandins and prostacyclin. Consequently, these molecules induce a state of inflammation via inducing hyperalgesia, hypercoagulation, fever and vasodilation (Vane and Botting, 1998). COX1 can be found predominantly within the gastric mucosa, whilst COX2 resides mostly within sites of inflammation. This makes COX2 inhibitors such as Celecoxib less prone to induce gastric bleeding which is an advantage compared to Aspirin.

3.1.2. Celecoxib

As can be seen in Table 2, there were three studies assessing the efficacy of adjunctive Celecoxib medication in treatment resistant bipolar depression. Two studies evaluated Celecoxib augmentation on Escitalopram (Halaris et al., 2020; Edberg et al., 2018), the third one explored augmentation on a stable dose of a mood stabiliser or atypical antipsychotic medication (Nery et al., 2008). All three showed a greater improvement in HAM-D scores in the Celecoxib augmentation group (Halaris et al., 2020; Nery et al., 2008), although the study combining

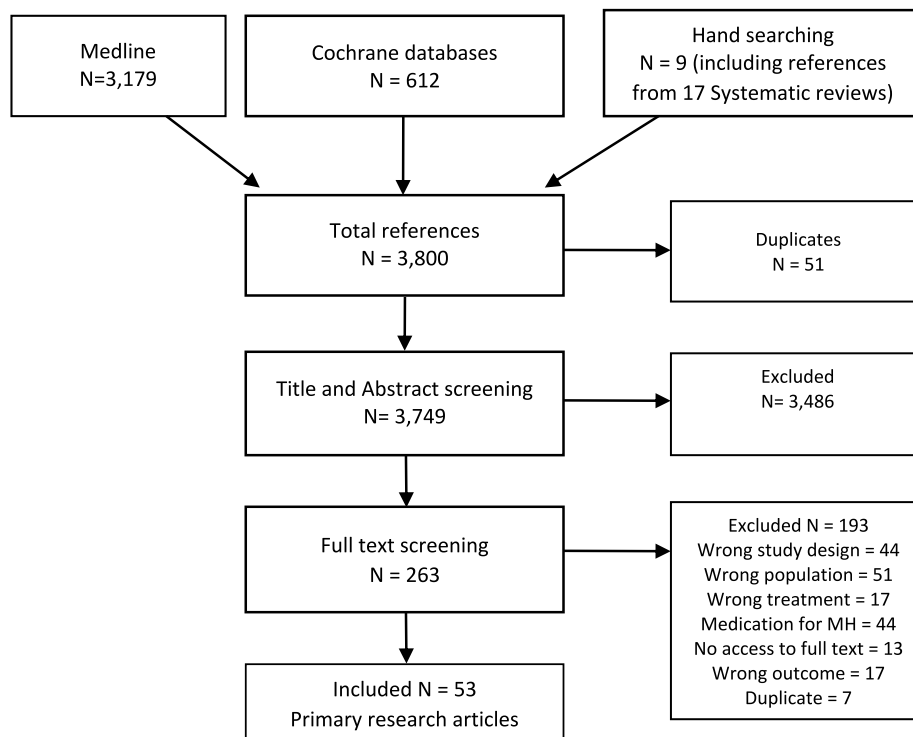


Fig. 1. Prisma diagram.

Celecoxib with a mood stabiliser or atypical antipsychotic medication only demonstrated this at one time point (week 1) and the benefit was not maintained by the study end point (Nery et al., 2008). One study assessed the efficacy of Celecoxib (400 mg daily) as an adjunctive treatment to Sodium Valproate in bipolar mania and showed a significant reduction in manic symptoms with Celecoxib compared to placebo (Arabzadeh et al., 2015).

3.1.3. Acetylsalicylic acid (Aspirin)

There was one study which assessed efficacy of Aspirin in bipolar depression, assessing it both alone and in combination with N-Acetylcysteine as an adjunct to treatment as usual (TAU) that consisted of Lithium, antipsychotics, antidepressants, or anticonvulsants. There was a modest benefit in treatment response rate in combination, but Aspirin alone did not show any benefit (Bauer et al., 2018).

3.1.4. Minocycline

Within the CNS, the tetracycline antibiotic Minocycline has been shown to have anti-inflammatory, antioxidant and neuroprotective effects. In the context of inflammation of unknown origin, the mechanism remains largely unknown; however, Minocycline is thought to inhibit neutrophil migration, degranulation, oxygen-free radical production and nitric oxide release. Consequently, this inhibits glutamate mediated ecotoxicity within microglia, preventing the release of inflammatory cytokines such as IL-6 and TNF α (Elewa et al., 2006).

Two studies examined the efficacy of Minocycline in bipolar depression. Both studies examined Minocycline alone and alongside another anti-inflammatory agent (with Celecoxib or with Aspirin) as an adjunct to TAU (Husain et al., 2020; Savitz et al., 2018) that consisted of mood stabiliser, antipsychotic, antidepressant or anxiolytics. Neither study found a benefit for Minocycline alone; however, Savitz et al. found that participants receiving both Minocycline and Aspirin had a better treatment response rate than those receiving double placebo and participants with higher IL-6 levels responded better than those with lower IL-6 levels (Savitz et al., 2018).

3.1.5. Cytokine inhibitors

Cytokine inhibitors refer to any agent that inhibits the function of inflammatory cytokines, thus inhibiting the inflammatory cascade, either by targeting the cytokine molecule or its receptor (Weckmann and Alcocer-Varela, 1996). This review includes anti-TNF α molecules infliximab and adalimumab, the anti interleukin-6 antibody Tocilizumab and the anti interleukin-1 molecule anakinra.

The effect of Infliximab as an adjunct to TAU with a variety of medications was explored in a study performed in 60 patients with bipolar depression and evidence of inflammation (CRP>5, obesity, DM, IBD or rheumatological disorder). No difference between Infliximab and placebo was seen overall, but a secondary analysis demonstrated a significant response to Infliximab in a subset of participants with a history of childhood maltreatment, mainly physical abuse (McIntyre et al., 2019).

3.1.6. Other

Pioglitazone is prescribed in diabetes to improve the control of glucose and lipid metabolism. It has also demonstrated anti-inflammatory properties by inhibition of NF- κ B (Kaplan et al., 2014). NF- κ B is a protein complex involved in transcriptional induction of inflammatory chemokines, cytokines and leukocyte recruitment (Liu et al., 2017).

One study examined the efficacy of Pioglitazone in bipolar depression (in bipolar type 1 disorder) as an adjunct to Lithium (Zeinoddini et al., 2015). This found a small but significantly greater reduction in HDRS scores in the Pioglitazone group compared to placebo.

3.2. Mood disorders: major depressive disorder

3.2.1. Celecoxib

In major depressive disorder, five studies assessed the efficacy of Celecoxib as an adjunctive treatment to antidepressant therapy (Sertraline, Reboxetine, Fluoxetine or Vortioxetine) as shown in Table 3. Four studies showed a greater decrease in HAMD score with Celecoxib (Abbasi et al., 2012; Akhondzadeh et al., 2009; Muller et al., 2006; Majd

Table 2

Summary of papers assessing anti-inflammatory medications in the treatment of Bipolar affective disorder (alphabetically by medication).

Reference	Sample size	Condition	Population demographics	Adjunctive treatment Medication	Daily dose	contrast	Duration	Primary Outcome	Main findings
Bauer et al 2018	36	Bipolar depression	Mean age= 41.12yrs Gender: F= 62.5%	Acetylsalicylic acid (Aspirin) (+N-acetylcysteine)	100mg	Aspirin and placebo or NAC and placebo or Aspirin and NAC or Placebo and Placebo augmentation or to TAU (Lithium, antipsychotics, antidepressants, anticonvulsants)**	16 weeks	MADRS	Aspirin + NAC associated with higher probability of treatment response compared with either drug alone or placebo. NAC + Aspirin treatment response 67% compared to placebo 55%, NAC alone 57% and Aspirin alone 33%
Savitz et al., 2018	99	Bipolar depression	Mean age= 41.75yrs Gender: F=73.25%	Minocycline Acetylsalicylic acid (Aspirin)	200mg 162mg	Aspirin and placebo or Minocycline and placebo or Minocycline and Aspirin or placebo and placebo augmentation to TAU (mood stabiliser, antipsychotic, antidepressant or anxiolytic)**	6 weeks	MADRS	No benefit from Minocycline alone, though participants with higher IL-6 levels responded better than those with lower IL-6 levels. Participants receiving Minocycline plus Aspirin had a better response rate compared with participants receiving double placebo ($\chi^2=3.35, p=0.034$, odds ratio (OR)=2.93, 95% confidence interval (CI)=0.93–10.08, NNT=4.7
Arabzadeh et al., 2015	48	Bipolar mania	Mean age= 31.4yrs Gender: F= 34.8% Mean duration of illness= 9.1 yrs Baseline YMRS= 33.1	Celecoxib	400mg	Celecoxib or placebo augmentation to Sodium Valproate 800mg/day PRN Lorazepam to manage agitation	6 weeks	YMRS	Significantly greater reduction in mania symptoms in Celecoxib group (mean change - 29.78 +/- 21.78 for Celecoxib group and -21.78 +/- 7.16 for placebo group. Mean difference - 8.00 (95% CI -12.18 to -3.81). A significantly higher remission rate (but not response rate) was observed in the Celecoxib group (87.0%) compared to the placebo group (43.5%) at Week 6 (p = 0.005)
Halaris et al 2020	65	Bipolar depression	Mean age= 55yrs Gender: F= 51%	Celecoxib	400mg	Celecoxib or placebo augmentation to Escitalopram 20mg/day (+ mood stabiliser and/or antipsychotic as indicated)*	8 weeks	HAMD17	Celecoxib group improved more as reflected in a significantly lower HAM 17 scores at week 1, 4 and 8 (p=0.002). Higher rates of response (OR 4.13 (95 CI: 1.03–18.48 p=0.021) and remission (OR 14.34 (95% CI: 2.59–153.17 p<0.0005) in Celecoxib group
Edberg et al 2018	47	Bipolar depressive disorder	Mean age= 43.3yrs Gender: F= 59.6%	Celecoxib	400mg	Celecoxib or placebo augmentation to Escitalopram 10–20mg/day (+ usual mood stabiliser/antipsychotic medication)**	8 weeks	HAMD17	The CBX group had significantly lower HAMD-17 scores vs. placebo at week 4 (P = 0.026) and week 8 (P = 0.002) associated with reduced CRP in Celecoxib group
Nery et al 2008	32	Bipolar depression	Mean age= 41.7yrs Gender: F= 57.2% Baseline HAMD17= 21.95	Celecoxib	400mg	Celecoxib or placebo augmentation to TAU (at least 1 month of mood stabiliser, antipsychotic or antidepressant)**	6 weeks	HAMD17	Lower HAMD scores in Celecoxib group at week 1 (mean HamD score 11.4 (SD6.4) in Celecoxib group vs 17.9 (SD8.5) in placebo p=0.028 but no difference at other time points
Husain et al 2020	266	Bipolar depression	Mean age =35.0yrs Gender: F=29%	Minocycline Celecoxib	200mg 400mg	Minocycline and placebo or Celecoxib and placebo or Minocycline and Celecoxib or placebo and placebo augmentation to TAU (mood stabilisers,	12 weeks	HAMD-17	No significant effect, effect not moderated by CRP

et al., 2015), although one study only demonstrated this at week 4 and by the study end point at week 8 the difference from placebo was no longer statistically significant (Majd et al., 2015). One study found no significant difference between treatment groups overall (Baune et al., 2021).

3.2.2. Acetylsalicylic acid (Aspirin)

Two studies using Aspirin in major depressive disorder as an adjunct to Duloxetine or Escitalopram did not show any significant difference between Aspirin and placebo HAMD scores at 6 months; however, the Aspirin + Duloxetine group showed quicker improvement in HAMD scores and better remission rate than the Escitalopram + placebo group

(Zdanowicz et al., 2017). Another study providing augmentation of Aspirin with Citalopram had to be stopped prematurely because of adverse effects (severe anxiety and akathisia) (Ghanizadeh and Hedayati, 2014).

3.2.3. Minocycline

Three studies examined the efficacy of Minocycline as an adjunct to TAU with medication (Husain et al., 2017; Dean et al., 2017; Nettis et al., 2021). One study found a significant benefit for Minocycline. This finding was not replicated in the other two studies (Dean et al., 2017), although one of them that only included patients with elevated levels of peripheral inflammation (defined as CRP \geq 1 mg/L) found some evidence

						atypical and typical antipsychotics, SSRI, tricyclic, SNRI, NaSSA antidepressants, benzodiazepines)** Escitalopram most common.			
McIntyre et al 2019	60	Bipolar depression with evidence on inflammation (CRP>5, obesity, DM, IBD or rheumatological disorder)	Mean age= 45.9yrs Gender: F= 79% Baseline MADRS= 30.05	Infliximab (anti TNFa)	5mg/kg	Infliximab or placebo augmentation to TAU (mood stabiliser/ antipsychotic/ antidepressant)***	6 weeks (12 week follow up)	MADRS	No significant effect with Infliximab compared to placebo. In a secondary analysis, a significant response to Infliximab was observed in the subset of participants with a history of childhood maltreatment, mainly physical abuse (p=0.04)
Zeinodini et al 2015	48	Bipolar type 1, major depressive episode	Mean age = 32.7yrs Gender: F = 34.1% Baseline HDRS 23.07	Pioglitazone	30mg	Pioglitazone or placebo augmentation to Lithium only	6 weeks	HDRS	Significantly greater reduction was observed in HDRS scores in the Pioglitazone group compared to the placebo (mean difference at week 6 2.27, 95% CI -3.87 to 0.67, p=0.006)

All treatments as usual are specified unless not described in the publication itself. Generic medication names, between brackets if stated otherwise in article.

* One or more of the following medications for mood stabilization as indicated: Quetiapine, Lamotrigine, Divalproex sodium, Buspirone, Lorazepam, Topiramate, Clonazepam, Ziprasidone, Temazepam, Hydroxyzine, Oxcarbazepine, Alprazolam, Gabapentin, Carbamazepine, Asenapine, Risperidone, Olanzapine, Aripiprazole, Diazepam, Oxcarbazepine, Chlorpromazine, Zolpidem, Lurasidone.

** not specified

*** Lithium, sodium valproate, quetiapine, olanzapine with fluoxetine, lurasidone, lamotrigine, unspecified antidepressant.

Colour code: Green – positive findings; amber – inconclusive or positive findings in subgroup only; red – negative findings.

of benefit for Minocycline in the high inflammation group after stratification based on CRP levels above or below 3 mg/L (Nettis et al., 2021)

3.2.4. Cytokine inhibitors

Two studies examined the effect of cytokine inhibitors as an adjunct to TAU in major depression (Raison et al., 2013; Weinberger et al., 2015). One that examined the effect of Infliximab in 60 subjects with major depressive disorder did not find any benefit overall; but, found a greater response in HAMD score to Infliximab than placebo in subjects with evidence of inflammation (baseline hs-CRP concentration >5 mg/L) did have (Raison et al., 2013). A study of sleep parameters in a subset of this cohort found that subjects with high inflammation receiving Infliximab demonstrated improvement in sleep continuity and decreases in Stage 2 sleep (Weinberger et al., 2015).

3.2.5. Other

Statins primarily lower cholesterol via inhibition of HMG-CoA reductase, but they are also thought to reduce cytokine release and reactive oxygen species generation via inhibition of the Rho and Rac signalling pathways, respectively. Statins have also been identified to upregulate endothelial nitric oxide synthase, an enzyme essential to nitric oxide (NO) production. NO plays an important role in maintaining endothelial homeostasis, regulating inflammatory states and inducing vasodilation (Antonopoulos et al., 2012).

A study evaluating Simvastatin augmentation of Fluoxetine in major depression found a significant improvement in HDRS scores and faster response rates in the Simvastatin group over placebo (Gougol et al., 2015). Another study found a significant benefit for Atorvastatin over placebo augmentation of Citalopram, found a significant benefit for Atorvastatin (Haghighi et al., 2014). Pioglitazone augmentation of Citalopram was beneficial with a significantly greater reduction in HAMD, earlier response to treatment and greater remission rates in the Pioglitazone group at 6 weeks compared to placebo (Sepanjnia et al., 2012).

Pentoxifylline evokes its anti-inflammatory effects by inhibition of phosphodiesterase-4. Phosphodiesterase-4 regulates cAMP within many pro-inflammatory of the immune system, and hence the production of several inflammatory cytokines, including IL-1, IL-6, interferon-γ and TNFα (Ghasemnejad-Berenji et al., 2021). A study evaluating Pentoxifylline augmentation of Escitalopram found a significantly greater improvement in HAMD score in the Pentoxifylline group (El-Haggag et al., 2018).

3.3. Schizophrenia and psychotic disorders

3.3.1. Celecoxib

There were five studies assessing the efficacy of Celecoxib as an adjunct to antipsychotic treatment in schizophrenia, as shown in Table 4. Three studies reported a significant benefit on the PANSS with Celecoxib augmentation to Risperidone (Akhondzadeh et al., 2007; Müller et al., 2002; Zhang et al., 2021). One study of Celecoxib augmentation to Amisulpride did not find an effect on PANSS but did see an improvement in the secondary outcome clinical global impression (CGI) score (Muller et al., 2010). The remaining study did not report any benefit of Celecoxib augmentation to Risperidone or Olanzapine (Rapaport et al., 2005).

3.3.2. Acetylsalicylic acid (Aspirin)

Four studies considered the efficacy of Aspirin as an adjunct to usual antipsychotic treatment in schizophrenia. One study showed a significant reduction in total PANSS score and positive PANSS subscale compared with placebo at 12 weeks (Laan et al., 2010); one also showed reduction in negative and general PANSS subscales at 6 weeks (Attari et al., 2017). Two studies (reported in the same paper) did not show any benefit of Aspirin on PANSS by 16 weeks (Weiser et al., 2021).

3.3.3. Minocycline

Six of nine studies exploring the efficacy of Minocycline in schizophrenia found benefit for negative symptoms (Levkovitz et al., 2010; Chaudhry et al., 2012; Zhang et al., 2018; Khodaie-Ardakani et al., 2014; Liu et al., 2014, 2018). One examined the effect of Minocycline augmentation to atypical antipsychotics on negative symptoms in early phase schizophrenia within the first 5 years of symptoms and found quicker response to treatment and a significant improvement on SANS, CGI, and executive functioning (Levkovitz et al., 2010). Another early phase study found effect of Minocycline added to TAU with medication on negative symptoms as a significant reduction in the PANSS negative subscale at 12 months (Chaudhry et al., 2012). Low dose (100 mg daily) and high dose (200 mg daily) Minocycline as an adjunct to Risperidone was found to effectuate a significant reduction in both SANS and PANSS negative symptom scales at 12 weeks (Zhang et al., 2018), and the clinical improvement correlated with reduction in serum IL-1B and IL6. A fourth study showed a quicker response to treatment and a significant reduction in PANSS negative subscale as well as total PANSS score with

Table 3

Summary of papers assessing anti-inflammatory medications in the treatment of major depressive disorder (alphabetically by medication).

Reference	Sample size	Condition	Population demographics	Adjunctive treatment Medication	Daily dose	contrast	Duration	Primary Outcome	Main findings
Zdanowicz et al 2017	40	Major depressive disorder (1 st or second episode)	Mean age=40.33yrs Gender: F= 83% Mean HDS = 23.83	Acetylsalicylic acid (Aspirin)	100mg	Aspirin augmentation to Duloxetine and placebo or Escitalopram and placebo (dose not stated)	6 months	Hamilton depression scale	No significant difference between Aspirin and placebo groups. Duloxetine + Aspirin subgroup showed a more rapid improvement in HDS score at 2 months (t=-3.114, p=0.01), in CGI score at 5 months (t=-2.119, p=0.05), and a better remission rate ($\chi^2=6.296$, p 0.012) than the Escitalopram + placebo subgroup
Ghanizadeh et al 2014	10	Major depressive disorder	Not stated	Acetylsalicylic acid (Aspirin)	160mg	Aspirin or placebo augmentation to Citalopram 20mg/ day only	6 weeks (stopped early at 14 days)	Hamilton depression scale	Results of primary outcome measures not reported. 8 out of 10 patients showed severe anxiety and akathisia - medication discontinued within 14 days of trial. Three patients were hospitalized due to anxiety and akathisia. Two patients reported suicidal behaviour.
Haghghi et al 2014	60	Major depressive disorder	Mean age = 32.3yrs Gender: F=47%	Atorvastatin	20mg	Atorvastatin or placebo augmentation to Citalopram 40mg/day only	12 weeks	HDRS	HDRS scores decreased more over time in the Atorvastatin than in the placebo group (mean difference in HDRS at 12 weeks 2.4). Partial remission was significantly more frequently observed in the Atorvastatin than in the placebo group ($\chi^2=5.19$, p=0.023)
Abbasi et al 2012	40	Major depressive disorder	Mean age= 34.5yrs Gender: F= 32.5%	Celecoxib	400mg	Celecoxib or placebo augmentation to Sertraline 200mg/day only	6 weeks	HAMD	Significantly lower HAMD scores in Celecoxib group compared with placebo (mean difference 3.35(95% CI 1.08 to 5.61), P=0.005). This was associated with reduced IL-6. 95% patients in Celecoxib group responded compared to 50% placebo group (p=0.003), 35% patients in the Celecoxib group experienced remission (HAMD ≤ 7) compared to 5% in the placebo group (p=0.04)
Muller et al 2006	40	Major depressive disorder	Mean age= 44.4yrs Gender: F= 50% Baseline HAMD = 25.0	Celecoxib	400mg	Celecoxib or placebo augmentation to Reboxetine 4-10mg/day only	6 weeks	HAMD	Significantly greater improvement in HAMD over time in Celecoxib group Mean decrease in HAMD score 14.0 in Celecoxib group compared to 8.1 in placebo group. 75% of patients in the Celecoxib group were responders compared to 45% in the placebo group (p<0.053)
Akhondzadeh et al 2009	40	Major depressive disorder	Mean age=34.25yrs Gender: F= 62.5% Baseline HAMD= 22	Celecoxib	400mg	Celecoxib or placebo augmentation to Fluoxetine 40mg/day only	6 weeks	HAMD17	Significantly greater improvement in HAMD score: mean change in Celecoxib group -13.20 (SD4.26) compared to -10.20 (SD 3.77) in placebo group (p=0.02). 90% of Celecoxib group were responders versus 50% in placebo group (p=0.01), 35% of Celecoxib group experienced remission versus 5% of placebo group (p=0.04)
Majd et al 2015	30	Major depressive disorder – first episode	Mean age 35.5yrs Gender: F=100%	Celecoxib	400mg	Celecoxib or placebo augmentation to Sertraline up to 100mg/day only	8 weeks	HAMD17	Celecoxib group showed significantly greater decrease in HAMD score compared to placebo at 4 weeks (-13.7 SD3.8 in Celecoxib group and -8.8 SD4.5 in placebo, p<0.05) but by 8 week the difference was no longer statistically significant (-18. SD3.4 in Celecoxib group, -15.8 SD5.2 in placebo group)
Baune et al 2021	119 (39 with evidence of low grade	Major depressive disorder (MADRS >20)	Median age 47 years 42.02% male	Celecoxib	200mg daily	Celecoxib or placebo augmentation to Vortioxetine	6 weeks	MADRS	No significant difference between treatment groups overall. Pre-treatment hsCRP levels did not identify individuals who could benefit from celecoxib

Minocycline augmentation of Risperidone (Khodaie-Ardakani et al., 2014). Two studies of Minocycline augmentation of Risperidone showed a significant decrease in SANS, PANSS negative symptom score and PANSS total score in the Minocycline group at 16 weeks (Liu et al., 2014, 2018).

Three studies did not show any benefit on psychotic symptoms of Minocycline in the treatment of schizophrenia (Kelly et al., 2015; Weiser et al., 2019; Deakin et al., 2018). Two were multicentre trials comparing Minocycline augmentation of usual antipsychotic treatment in 200 and 207 participants respectively (Weiser et al., 2019; Deakin et al., 2018). However, a third study that looked at Minocycline as an adjunct to Clozapine did not show improvement of psychotic symptoms, but

reported significant improvements in depressive, anxiety and cognitive symptoms (Kelly et al., 2015).

3.3.4. Cytokine inhibitors

One study examining Tocilizumab, an IL6 receptor antagonist, in the treatment of schizophrenia as an adjunct to usual antipsychotic treatment did not find any significant difference in the PANSS at 12 weeks (Girgis et al., 2018). One study examined Adalimumab, a TNF- α inhibitor, as an adjunctive treatment to Risperidone, and did find significantly lower total PANSS scores, negative subscale score and general psychopathology subscale scores in the Adalimumab group at 8 weeks (Motamed et al., 2022).

	inflammation hsCRP >3mg/L, , 80 with hsCRP ≤3mg/L)									
Weinberger et al 2014	36	Treatment resistant depression	Mean age= 43.4yrs Gender: F= 60% Baseline HAMD= 24.3	Infliximab (anti-TNFa)	5mg/kg	Infliximab augmentation to TAU (antidepressant +/- antipsychotic / mood stabiliser / hypnotics**	6 weeks	Nocturnal polysomnographic sleep measures	Depressed subjects with high inflammation (CRP>5) receiving Infliximab demonstrated improvement in sleep continuity (decreased spontaneous arousals, decreased WASO, and increased sleep efficiency) and decreases in Stage 2 sleep as well as decreases in sleep period time compared to placebo.	
Raison et al 2013	60	Treatment resistant MDD	Mean age= 43.4yrs. Gender: F= 67% Baseline HAMD= 23.85	Infliximab (anti-TNFa)	5mg/kg	Infliximab or placebo augmentation to TAU **	6 weeks	HAMD17	No differences in change in HAM-D scores over time were found between treatment groups. There was a significant interaction among treatment, time, and log hs-CRP concentration: A baseline hs-CRP concentration >5 mg/L was associated with a greater decrease (mean difference 3.1 points) in HAM-D scores in Infliximab patients than placebo-treated patients (t302 = 2.65, P = .01).	
Husain et al 2017	41	Treatment resistant Major depressive disorder	Mean age= 37.5yrs Gender: F= 50% Illness duration: Majority >12m Mean baseline HAMD =33.5	Minocycline	200mg	Minocycline or placebo augmentation to TAU (antidepressant +/- antipsychotic / mood stabiliser*** (except valproate) /	12 weeks	HAMD-17	Significant reduction in HAMD in Minocycline group compared with placebo at 12 week: mean difference in HAMD 18.1 (95% CI -24.7 - -11.5, standardised effect size = -1.21, p < 0.001) 63% of the Minocycline group responded to treatment compared with 22% of the placebo group (OR: 5.5, p = 0.035)	
Nettis et al 2021	39	Treatment resistant major depressive disorder with CRP>1	Mean age= 45yrs Gender: F= 56% Mean illness duration= 19.5yrs Mean baseline HAMD= 18	Minocycline	200mg	Minocycline or placebo augmentation to TAU (antidepressant +/- antipsychotic / mood stabiliser)*	4 weeks	HAMD-17	No significant difference overall but stratification for CRP levels showed significant effect in subgroup with CRP ≥3. Mean change in HAMD-17 score 12.00±6.45 for Minocycline versus 3.50 ± 4.34 for placebo (p=0.002).	
Dean et al 2017	71	Major depressive disorder	Mean age= 49.4yrs Gender: F= 66% Mean illness duration= 13.9yrs Mean Baseline MADRS= 31.7	Minocycline	200mg	Minocycline or placebo augmentation to TAU (antidepressant +/- antipsychotic / mood stabiliser / Benzodiazepine**	12 weeks	MADRS	No significant difference for primary outcome but significant improvement in quality of life measures	
El-Haggag et al 2018	80	Major depressive disorder	Mean age=32.91yrs Gender: F= 50.7% Baseline HAMD= 19.6	Pentoxifylline	800mg	Pentoxifylline or placebo augmentation to Escitalopram 20mg/day	12 weeks	HAMD	Significantly greater improvement in HAMD score in Pentoxifylline group compared to placebo (mean difference -3.49, p= 0.000). This was associated with reduction TNF-α, IL-6, IL-10. 85% of the patients in the PTX group and 41% in the control group were remitted after 12 weeks (p = 0.023) and 92% in PTX group were responders versus 58% in placebo group (p= 0.000)	
Sepanjnia et al 2012	40	Major depressive disorder	Mean age= 32.1yrs Gender: F= 73% Baseline HAMD= 25.4	Pioglitazone	15mg	Pioglitazone or placebo augmentation to Citalopram 30mg/day +/- 10mg/day Chlordiazepoxide	6 weeks	HAMD	Significantly greater reduction in HAMD in Pioglitazone group at 6 weeks compared to placebo (mean difference in HAMD scores -3.4 (95% CI-5.6 to -1.2, p0.004)	
Gougol et al 2015	48	Major depressive disorder	Mean age= 35.3yrs Gender: F= 60%	Simvastatin	20mg	for those with sleep disturbance. Simvastatin or placebo augmentation to Fluoxetine 40mg/day only	6 weeks	HDRS	Significant difference in HDRS scores at 2, 4 and 6 weeks (mean difference at 6 weeks 4.81, p=0.02). 90% of patients in the Simvastatin group and 59% of patients in the placebo group experienced a response to treatment (p=0.01). There was no difference in remission rates.	

All treatments as usual are specified unless not described in the publication itself. Generic medication names, between brackets if stated otherwise in article.

* selective serotonin reuptake inhibitors, tricyclics, monoamine oxidase inhibitors, noradrenergic and specific serotonin antagonists and serotonin noradrenaline reuptake inhibitors, unspecified mood stabilisers, antipsychotics and benzodiazepines

** not specified

*** selective serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, noradrenergic and specific serotonin antagonists and serotonin noradrenaline reuptake inhibitors, unspecified mood stabilisers and antipsychotics

Colour code: Green – positive findings; amber – inconclusive or positive findings in subgroup only; red – negative findings.

Table 4
Summary of papers assessing anti-inflammatory medications in the treatment of Schizophrenia (alphabetically by medication).

Reference	Sample size	Condition	Population demographics	Medication	Daily dose	Adjunctive treatment (both study arms)	Duration	Primary Outcome	Main findings
Laan et al 2010	70	Schizophrenia (<5 years duration, >60 on PANSS)	Mean age=31.1yrs Gender: M= 83% Mean duration of illness= 3.75 yrs Mean baseline PANSS= 72.1	Acetylsalicylic acid (Aspirin)	1000mg	Aspirin or placebo augmentation to TAU (antipsychotic) ^a	12 weeks	PANSS	Significant reduction in symptoms in Aspirin group: 4.86-point (95% CI, 0.91 to 8.80) reduction in total PANSS score and 1.57-point (95% CI, 0.06 to 3.07) reduction in PANSS positive subscale compared with placebo
Attari et al 2017	60	Schizophrenia	Mean age=32.8yrs Gender: M=78.3%	Acetylsalicylic acid (Aspirin)	325 mg or 500mg	Aspirin or placebo augmentation to Antipsychotic (Olanzapine, Haloperidol, Risperidone, or Chlorpromazine) ^b	6 weeks	PANSS	Significant improvement in positive, negative and general symptom scales in Aspirin group compared to placebo. This benefit was seen at 6 weeks as well as 4 weeks follow up after stopping Aspirin (mean change scores not given)
Weiser et al 2021 Study 1	200	Schizophrenia (at least 2 prior psychotic episodes and/or had been continually ill for at least 6 months)	Mean age 42.85 years Gender 51.5% male	Acetylsalicylic acid (Aspirin)	1000mg	Treatment as usual (atypical or typical antipsychotic)	16 weeks	PANSS	No significant difference between groups
Weiser et al 2021 Study 2	160	Schizophrenia (at least 2 prior psychotic episodes and/or had been continually ill for at least 6 months) and CRP>1mg/l at baseline	Mean age 41.55 years Gender 51.9% male	Acetylsalicylic acid (Aspirin)	1000mg	Treatment as usual (atypical or typical antipsychotic)	16 weeks	PANSS	No significant difference between groups
Motamed et al 2022	40	Schizophrenia (>2 years duration)	Mean age 35.72 years Gender = 65% male Baseline total PANSS score 99.9	Adalimumab (anti TNFa)	40mg at week 0 and week 4	Risperidone 2mg daily, increased by 2mg per week according to response to maximum of 6mg daily	8 weeks	PANSS	Adalimumab group showed significantly lower PANSS total score at week 4 (69.20 ±SD14.97 vs 78.55 ±SD 12.08, p=0.036) and week 8 (52.15 ±SD 11.29 vs 65.90 ±SD 13.23 p=0.001) Significantly lower PANSS negative subscale score and general psychopathology subscale score but no difference in positive subscale score
Müller et al 2002	50	Schizophrenia	Mean age=35.7yrs Gender: M= 50% Baseline PANSS= 73.6	Celecoxib	400mg	Celecoxib or placebo augmentation to Risperidone 2-6mg/day only	5 weeks	PANSS	Significant benefit on PANSS total score at weeks 2-4 (mean change scores not available)
Akhondzadeh et al 2007	60	Schizophrenia	Mean age=33.7yrs Gender: M= 58% Mean duration of illness= 7.89 yrs	Celecoxib	400mg	Celecoxib or placebo augmentation to Risperidone 6mg/day only	8 weeks	PANSS	Significantly greater improvement in total PANSS, positive subscale and general symptom scale in Celecoxib group. Changes in PANSS total score at 8 weeks -43.70±SD15.91 in Celecoxib group and -29.16±SD14.84 for placebo group (p<0.001)
Zhang et al 2021	100	Schizophrenia (1 st episode, drug naïve)	Mean age 29.15years 67.8% male Baseline total PANSS score 92.0	Celecoxib	200mg	Risperidone 1mg daily, dose adjusted over two weeks to 4 mg to 6 mg/day according to response	6 weeks	IDO levels at week 6, secondary outcome PANSS	Celecoxib group showed a significantly greater improvement in PANSS total scores (58.50 ± 12.35 in celecoxib group vs. 67.57 ± 11.84 in placebo group, P<0.001) negative subscale (14.57 ± 4.41 vs 18.13 ± 6.01, p=0.002) and positive subscale scores (15.76 ± 4.66 vs 19.43 ± 5.08, p<0.001)

3.3.5. Other

Other medications trialled in schizophrenia were Pravastatin, Simvastatin, Pioglitazone, Methotrexate, Hydroxychloroquine and Prednisolone. A trial of Pravastatin augmentation of TAU did not show any significant benefit in outcomes except for a significant decrease in the PANSS positive symptoms score at 6 weeks; however, this was not seen at the 12-week study endpoint (Vincenzi et al., 2014). Simvastatin augmentation of TAU resulted in lower total PANSS scores in the Simvastatin group at 6 and 24 months; however, there were no significant difference at pre-defined end point of 12 months (Sommer et al., 2021). A trial of Pioglitazone as an adjunct to Risperidone showed a significant reduction in negative subscale and total PANSS at 8 weeks in the Pioglitazone group compared to placebo (Iranpour et al., 2016).

Methotrexate has been shown to inhibit NF-κB activation, increase T-cell sensitivity to apoptosis and increase extracellular adenosine which binds to cell surface receptors to prevent pro-inflammatory signalling (Chronstein and Aune, 2020). A recent study of Methotrexate as an adjunct to TAU had a statistically significant effect on PANSS Positive Subscale but no significant effect on negative subscale and overall, the difference in total PANSS score was of borderline significance (Chaudhry et al., 2020). Hydroxychloroquine induces its anti-inflammatory effects by inhibiting activation of the toll-like-receptor-9, a receptor that triggers a pro-inflammatory response to microbial products (Kuznik et al., 2011). The study of Hydroxychloroquine as an adjunct to typical antipsychotic treatment in 61 participants showed no significant benefit (Desta et al., 2002). The study of

Muller et al 2010	50	Schizophrenia (<2 years duration)	Mean age=28.6yrs Gender: M=60% Mean duration of illness= 15.5 months Baseline PANSS= 95.2	Celecoxib	400mg	Celecoxib or placebo augmentation to Amisulpride 200-1000mg/day only	6 weeks	PANSS	No significant effect on PANSS (trend to significance in PANSS negative subscale). Significant beneficial effect on CGI as secondary outcome.
Rapaport et al 2005*	35	Schizophrenia	Mean age=45.7yrs Gender: M=82.7% Baseline PANSS= 84.15	Celecoxib	400mg	Celecoxib or placebo augmentation to TAU (Risperidone or Olanzapine)	8 weeks	PANSS	No significant effect
Desta et al 2002	61	Schizophrenia, schizoaffective or schizophreniform disorder	Mean age=29.9yrs Gender: M=84%	Hydroxychloroquine	200mg	Hydroxychloroquine or placebo augmentation to TAU (typical antipsychotic) ^g	8 weeks	PANSS	No significant difference in PANSS
Chaudhry et al 2020	92	Schizophrenia schizoaffective disorder, psychosis not otherwise specified or schizophreniform disorder, within 5 years of diagnosis	Mean age=25.7yrs Gender: M=73%	Methotrexate	10mg once weekly	TAU (antipsychotic – first or second generation) ^g	12 weeks	PANSS	Methotrexate had a statistically significant effect on PANSS Positive Subscale (-2.94 (95% CI -5.10, -0.77) (p = 0.008), no significant change in PANSS negative scores and difference in total score was of borderline significance (p=0.05)
Levkovitz et al 2010	54	Schizophrenia (within first 5 years of onset)	Mean age=24.9yrs Gender: M=76.3% Mean baseline total PANSS= 81, mean PANSS negative score=22.5 mean SANS=43	Minocycline	200mg	Minocycline or placebo augmentation to Atypical antipsychotic (Risperidone, Olanzapine, Quetiapine, or Clozapine) equivalent to 200-600mg/day of Chlorpromazine	24 weeks	SANS	Significant effect on SANS (time x treatment effect size 0.46 p<0.01) but not PANSS negative symptom scale. Also showed significant effect on CGI and some cognitive subscales
Chaudhry et al 2012	144	Schizophrenia, schizoaffective disorder, psychosis NOS within first 5 years	Mean age=26.2yrs Gender: M=52% Mean baseline total PANSS=83 negative score= 22.3	Minocycline	200mg	Minocycline or placebo augmentation to TAU (antipsychotic) ^g	12 months	PANSS negative and positive subscale	Significant effect on negative subscale of PANSS: mean improvement in negative symptoms for the Minocycline group was 9.2 and in the placebo group 4.7, an adjusted difference of 3.53 (s.e. 1.01) 95% CI: 1.55, 5.51, p < 0.001
Khodaie-Ardakani et al 2014	40	Schizophrenia, schizoaffective, psychosis NOS for more than 2 years	Mean age=39.9yrs Gender: M=72.5% Mean illness duration=19 yrs Mean baseline total PANSS=71.6 negative subscale= 17.4	Minocycline	200mg	Minocycline or placebo augmentation to Risperidone 6mg/day only	8 weeks	PANSS	Significant effect on negative subscale of PANSS (mean 12.70 SD 2.02 in Minocycline group versus 17.25 SD3.00 in placebo p<0.001) as well as general and total subscale
Zhang et al 2018**	75	Schizophrenia with negative symptoms	Mean age=33.0yrs Gender: M=50% Mean duration of illness= 6.1 yrs Mean baseline total PANSS= 78.78 PANSS negative score =26.3	Minocycline	100mg or 200mg	Minocycline or placebo augmentation to Risperidone 3-6mg/day +/- Lorazepam for insomnia or Trihexyphenidyl Hydrochloride for extrapyramidal symptoms	12 weeks	PANSS negative symptom subscale and SANS	Significant reduction in negative symptoms as well as some measures of cognitive functioning in high dose Minocycline (PANSS negative symptom change -5.6 in high dose Minocycline vs -3.6 in placebo, p=0.012 SANS score -13.64 vs -8.4 in placebo p=0.002). The clinical improvement correlated with reduction in serum IL-1B and IL6

Prednisolone augmentation of TAU did not show any benefit at 6 weeks or 12 months (Nasib et al., 2021).

3.4. SSRD: chronic fatigue syndrome

Only one study was found relating to SSRD as shown in Table 5. This study assessed the efficacy of Anakinra (an interleukin-1 antagonist) in 50 women with chronic fatigue syndrome. This was not an augmentation study as currently no pharmacological treatment for chronic fatigue syndrome exists. It did not find a clinically significant reduction in fatigue severity with Anakinra (Roerink et al., 2017).

3.5. Adverse events

Across all studies there was no difference in the incidence of serious drug side effects requiring hospitalisation, except in one study. The study evaluating Aspirin or placebo augmentation to Citalopram found that eight out of ten patients showed severe anxiety and akathisia from the early days of this trial, that necessitated discontinuation of the medication and hospitalization of three patients. Also, two patients reported suicidal behaviour after the onset of this trial (Ghanizadeh and Hedayati, 2014).

Only two studies reported a significant increase in side effects within the Celecoxib vs placebo group (Nery et al., 2008; Muller et al., 2006). Muller et al. (2006) reported 4 patients of 20 that developed hypertension, sleep-disturbance, difficulties in miction or erection and rash

			Mean baseline total PANSS= 81, mean PANSS negative score=22.5 mean SANS=43			Olanzapine, Quetiapine, or Clozapine) equivalent to 200-600mg/day of Chlorpromazine			significant effect on CGI and some cognitive subscales
Chaudhry et al 2012	144	Schizophrenia, schizoaffective disorder, psychosis NOS within first 5 years	Mean age=26.2yrs Gender: M=52% Mean baseline total PANSS=83 negative score=22.3	Minocycline	200mg	Minocycline or placebo augmentation to TAU (antipsychotic) ^f	12 months	PANSS negative and positive subscale	Significant effect on negative subscale of PANSS: mean improvement in negative symptoms for the Minocycline group was 9.2 and in the placebo group 4.7, an adjusted difference of 3.53 (s.e. 1.01) 95% CI: 1.55, 5.51, p < 0.001
Khodaie-Ardakani et al 2014	40	Schizophrenia, schizoaffective, psychosis NOS for more than 2 years	Mean age=39.9yrs Gender: M=72.5% Mean illness duration=19 yrs Mean baseline total PANSS=71.6 negative subscale= 17.4	Minocycline	200mg	Minocycline or placebo augmentation to Risperidone 6mg/day only	8 weeks	PANSS	Significant effect on negative subscale of PANSS (mean 12.70 SD 2.02 in Minocycline group versus 17.25 SD3.00 in placebo p<0.001) as well as general and total subscale
Zhang et al 2018**	75	Schizophrenia with negative symptoms	Mean age=33.0yrs Gender: M=50% Mean duration of illness= 6.1 yrs Mean baseline total PANSS= 78.78 PANSS negative score =26.3	Minocycline	100mg or 200mg	Minocycline or placebo augmentation to Risperidone 3-6mg/day +/- Lorazepam for insomnia or Trihexyphenidyl Hydrochloride for extrapyramidal symptoms	12 weeks	PANSS negative symptom subscale and SANS	Significant reduction in negative symptoms as well as some measures of cognitive functioning in high dose Minocycline (PANSS negative symptom change -5.6 in high dose Minocycline vs -3.6 in placebo, p=0.012 SANS score -13.64 vs -8.4 in placebo p=0.002). The clinical improvement correlated with reduction in serum IL-1B and IL6
Liu et al 2014	92	Schizophrenia (within first 5 years)	Mean age=27.6yrs Gender: M= 62% Mean duration of illness =2 years Mean baseline PANSS =82.3 Mean baseline SANS =60.37	Minocycline	200mg	Minocycline or placebo augmentation to TAU (Risperidone) +/- Alprazolam for insomnia or Trihexyphenidyl Hydrochloride for extrapyramidal symptoms or Propranolol for akathisia and tachycardia	16 weeks	SANS	Subjects receiving Minocycline had greater improvements on SANS total scores compared with placebo (mean change at week 16 -27.21 in Minocycline group compared to -13.4 in placebo group, p<0.001) as well as PANSS negative subscale scores (P<0.001), CGI severity scores (p=0.038) and PANSS total score (p=0.002). Rates of treatment response (43.6%) in the Minocycline group were significantly higher than those in the placebo group (10.0%) after 16 weeks of treatment.
Liu et al 2018	63	Schizophrenia (within first 5 years)	Mean age=27.4yrs Gender: M=62% Mean duration of illness =2 years Mean baseline total PANSS=82.3 Mean baseline SANS=62.25	Minocycline	200mg	Minocycline or placebo augmentation to TAU (Risperidone)	16 weeks	SANS	Significant greater decrease in SANS with Minocycline (Mean change in SANS score at 16 weeks -31.2 in Minocycline group compared to -14.8 in placebo group, p<0.001) as well as PANSS negative symptom score (p=0.001) and PANSS total score (p=0.006)
Kelly et al 2015	52	Schizophrenia or schizoaffective disorder, on Clozapine for at least 6 months with persistent positive symptoms	Mean age=42.4yrs Gender: M=74.5% Mean age illness onset= 19yrs Mean baseline BPR= 44.4 SANS= 31.5	Minocycline	200mg	Minocycline or placebo augmentation to Clozapine (at least 200mg/day)	10 weeks	BPRS	No significant effect

within the Celecoxib group for treatment of MDD (Muller et al., 2006). Nery et al. (2008) also reported that 2 of 14 patients within the Celecoxib group for treatment of bipolar depression developed rash (Nery et al., 2008). No studies reported an increased incidence of gastrointestinal side effects within the Celecoxib group.

4. Discussion

4.1. Summary of the findings

This scoping review finds evidence for effect of anti-inflammatory drugs across a wide range of medications and mental disorders. Since the 2014 review (Fond et al., 2014), in this rapidly evolving field there have been 37 further trials published, making this paper an important

update. It has shown that there is now a large body of evidence examining the use of a variety of anti-inflammatory medication in bipolar affective disorder, major depressive disorder and schizophrenia. However, the use of such medication in SSRD is not well researched. The results show that all but one study (Roerink et al., 2017) evaluate augmentation to other treatment and that there is heterogeneity in terms of the treatment to which an anti-inflammatory medication is augmented.

4.2. Mood disorders

Regarding bipolar disorder, the studies evaluating augmentation with Celecoxib to Sodium Valproate or to Escitalopram, or Pioglitazone augmentation to Lithium only, show significant improvement. However,

Deakin et al 2018	207	First episode of schizophrenia or schizoaffective psychosis, ongoing positive symptoms	Mean age=25.6yrs Gender: M=72.5% Mean baseline total PANSS=68.2 PANSS negative score=17.25	Minocycline	300mg	Minocycline or placebo augmentation to TAU (antipsychotic) ^f	12 months	Negative subscale of PANSS	No significant effect
Weiser et al 2019	200	Schizophrenia or schizoaffective disorder	Mean age=43.4yrs Gender 44% male Mean age of onset of illness=26yrs Mean baseline total PANSS=95.5	Minocycline	200mg	Minocycline or placebo augmentation to TAU (typical or atypical antipsychotic) ^f	16 weeks	PANSS	no difference in PANSS, CGI or cognition
Iranpour et al 2016	42	Schizophrenia >2 years	Mean age=37.5yrs Gender: M=69% Baseline total PANSS= 69.5 Mean duration of illness= 14.9years	Pioglitazone	15mg	Pioglitazone or placebo augmentation to Risperidone up to 6mg/day only	8 weeks	PANSS	Significant reduction in negative subscale and total PANSS at 8 weeks in Pioglitazone group compared to placebo group (mean difference =-3.25 (95%CI -4.89 to -1.60), p<0.001)
Vincenzi et al 2014	60	Schizophrenia	Mean age=43.6yrs Gender: M=63% Baseline total PANSS= 77.5	Pravastatin	40mg	Pravastatin or placebo augmentation to TAU (typical or atypical antipsychotic) ^f	12 weeks	PANSS Neuropsych battery	No significant differences at 12 weeks PANSS positive subscale significant at 6 weeks, attention/working memory tasks significantly improved in Pravastatin group at 6 weeks in subgroup of subjects with CRP>2
Nasib et al 2021	42	Schizophrenia (less than 7 years duration)	Mean age 30.12 years Gender 83.35% male	Prednisolone	40 mg/day for 3 days, then 30 mg/day for 4 days, followed by a decrease of 5 mg/day per week during the remaining 5 weeks	Treatment as usual (atypical or typical antipsychotic)	6 week treatment, 12 month follow up	PANSS	No significant differences between treatment groups. Study ended prematurely due to recruitment difficulties.
Sommer et al 2021	119	Schizophrenia, schizoaffective, schizophreniform disorder or psychotic disorder not otherwise specified (within 3 years of diagnosis)	Not stated	Simvastatin	40mg	Treatment as usual (typical or atypical antipsychotic)	12 months treatment, 24 months follow up	PANSS	At 6 and 24 months, simvastatin group had lower total PANSS scores than control, however no significant difference at pre-defined end point of 12 months
Girgis et al 2018	37	Schizophrenia	Mean age=42.5yrs Gender: M=70% Baseline total PANSS=72.31	Tocilizumab (anti IL-6)	8mg/kg	Tocilizumab or placebo augmentation to TAU (typical or atypical antipsychotic) ^a	12 weeks	PANSS	No significant difference. No association between CRP and outcome.

All treatments as usual are specified unless not described in the publication itself. Generic medication names, between brackets if stated otherwise in article.
 *A paper by Bresee et al., 2006 was identified in searches using data described by Rapaport and colleagues. No additional clinical outcome data were reported in this additional study.
 ** A further paper was published by Zhang and colleagues in 2019 with additional outcomes; these have been combined with the findings from their 2018 paper in this table.
^a unspecified but Clozapine, risperidone and olanzapine most common; ^b Dose equivalent to 100mg/day of chlorpromazine, ^c unspecified, ^d Unspecified, but olanzapine, risperidone, aripiprazole, and amisulpride most common, ^ehaloperidol, aripiprazole, olanzapine, perphenazine, paliperidone, fluphenazine, quetiapine, risperidone, chlorpromazine, paroxetine, bupropion, benzotropine, lurasidone, ziprasidone, lithium, sertraline and quetiapine, ^fLoxapine, thiothixene, perphenazine, chlorpromazine, clozapine, olanzapine, aripiprazole, quetiapine, ziprasidone, paliperidone, risperidone. Colour code: Green – positive findings; amber – inconclusive or positive findings in subgroup only; red – negative findings.

studies evaluating augmentation with other anti-inflammatory medication such as Aspirin, Minocycline or Infliximab on usual treatment show negative or inconclusive results.

This might be explained by different disease profiles. For example, the presence or absence of psychotic symptoms and acuity of disease may affect the choice of medication. Also, the choice of mood stabiliser can be associated with illness phase, for example some medications are provided in early stages of the illness, and others are second- or third-line medications. Allowing all available medications in TAU therefore neglects acuity of the illness, which should be taken into account. Furthermore, patients may have had an adverse reaction to a particular

mood stabiliser and therefore receive another one, which may be related to their genetic profile. These factors may cause ambiguous results when anti-inflammatory agents are augmented to miscellaneous medications.

A variety of other medications were evaluated in several rather small studies. Aspirin seemed effective if combined with N-Acetylcysteine or Minocycline, but not as a standalone treatment. Minocycline was effective especially if provided to patients with elevated inflammation markers. One study exploring Infliximab in case of elevated inflammation markers found effect in a participants with a history of childhood maltreatment only (McIntyre et al., 2019). To control for such variety to enable comparison, studies are needed augmenting these

Table 5

Summary of papers assessing anti-inflammatory medications in the treatment of Somatic Symptom Related Disorders.

Reference	Sample size	Condition	Population demographics	Medication	Daily dose	Contrast	Duration	Primary Outcome	Main findings
Roerink et al 2017	50	Chronic fatigue syndrome	Mean age=31 yrs Gender: F=100%	Anakinra (anti IL-1)	100mg daily	Anakinra compared to placebo	4 weeks	CIS-fatigue subscale	No significant difference

Colour code: Green – positive findings; amber – inconclusive or positive findings in subgroup only; red – negative findings.

anti-inflammatory medications to single psychotropic medications such as Escitalopram, Sodium Valproate or Lithium only.

Currently, there is evidence for the effect of Celecoxib or Pioglitazone augmentation in bipolar disorder, but no firm conclusion can be drawn regarding the other anti-inflammatory medications that were evaluated.

Similarly, in major depressive disorder, the majority of studies found benefit for Celecoxib augmentation of SSRI treatment. A few trials reported effect of Minocycline in treatment resistant depression, especially for those participants with elevated inflammation markers. Infliximab was also found to be effective in case of elevated inflammation markers. Trials evaluating augmentation with Simvastatin, Atorvastatin, Pioglitazone and Pentoxifylline to Escitalopram or Fluoxetine all showed effect. This supports evidence from large scale observational studies which have found lower rates of depression in patients taking statins (Redlich et al., 2014). In general, it is striking that studies augmenting monotherapy with SSRIs such as Escitalopram, Sertraline or Fluoxetine with anti-inflammatory medication in mood disorders have shown benefit. This may indicate a synergism in mechanism between the anti-inflammatory medication and the SSRI.

4.3. Schizophrenia

The findings of studies examining Celecoxib in Schizophrenia appear more mixed; studies augmenting Risperidone with Celecoxib show significant improvement in young patients with schizophrenia; however, a study evaluating Celecoxib in patients receiving Risperidone or Olanzapine, of higher average age, was inconclusive. Likewise, studies looking at Aspirin in schizophrenia have shown benefit in young patients, but not in patients with average age over 30 years. Such an age effect does not apply for Adalimumab, suggesting that age may be relevant in effect of medication for vascular inflammation like Celecoxib and Aspirin, but not in a TNF α blocker or antibiotics.

Studies evaluating Simvastatin and Prednisolone in schizophrenia showed no improvement.

Minocycline appeared to have a beneficial effect on negative symptoms in schizophrenia in the majority of early studies. However, the two most recent studies (Weiser et al., 2019; Deakin et al., 2018) did not see any benefit. These studies were well designed with larger sample sizes than previously; however, there was no evidence of inflammation within the study populations and the authors highlight that the longer duration of illness may have meant that any putative neuroinflammation had ceased by the time of participation in the study, as discussed below.

The effect of Minocycline augmentation in schizophrenia is more convincing than in other disorders and this might suggest a different underlying mechanism for treatment success than in the other main illness groups. This effect appears especially in young patients. These findings warrant further exploration of different anti-inflammatory treatment pathways for schizophrenia and mood disorder.

4.4. Therapeutic mechanisms

The mechanism in which augmentation with anti-inflammatory agents to regular psychiatric medication improves psychiatric symptoms remains largely uncertain. Multiple neuro-inflammatory pathways have been implicated in depression (Woelfer et al., 2019), bipolar

disorder (Benedetti et al., 2020) and schizophrenia (Müller et al., 2015). It may be that adding an anti-inflammatory offers an approach to improve the mental disorder from two ends: by decreasing the inflammation that helped generate the disorder, and by directly improving the symptoms that come from it. Moreover, psychotropic medications may exert an effect on inflammation (Sugino et al., 2009; Al-Amin et al., 2013; Hamer et al., 2011; Basterzi et al., 2005; Giridharan et al., 2020) and this may vary between drug classes; therefore, synergistic mechanisms may occur. This is supported by the finding that most of the studies that stratified by inflammatory markers found better efficacy in those patients who had evidence of inflammation at baseline: Nettis et al. found an effect for Minocycline in depression only in the subgroup of patients with CRP>3 (Nettis et al., 2021). Higher baseline IL-6 levels also predicted response. Similarly, Savitz et al. found patients with bipolar depression with higher IL-6 levels at baseline responded better to Minocycline (Savitz et al., 2018). Raison and colleagues observed improvement with Infliximab therapy only in depressed patients with an hsCRP >5 mg/l (Raison et al., 2013) Further research is needed to explore this.

The medications included in this review target both upstream and downstream inflammatory pathways. The Cox-2 inhibitor, Celecoxib is an example of a downstream inhibitor that has shown particular therapeutic promise in this review. This might suggest that the prostaglandin pathway plays an important role in therapeutic mechanisms of anti-inflammatories in psychiatric disease, especially major depressive disorder (Chu et al., 2017).

Regarding the clear advantage of augmentation with Minocycline in psychosis, this may in a similar way act on the CNS inflammation by improving microglia function; but also, it may be that the effect of Minocycline is related to antibiotic effects on an as yet unidentified bacteria that plays a role in the development or the persistence of schizophrenia-like psychotic symptoms. Although epidemiological associations between schizophrenia and exposure to infectious agents including Toxoplasmosis and cat scratch disease have been found, a causal link has remained elusive (Endres et al., 2020, 2022; Fan and Ali, 2020; Fuglewicz et al., 2017). There may also be effects on translocation of bacteria across the gut wall, thus influencing the brain-gut axis (Nemani et al., 2015). The positive effect of Minocycline warrants further research into the mechanism.

The effect of cytokine inhibitors may be result of a direct effect on pro-inflammatory cytokines, and further research is needed to explore this. For example, a study on Conversion Disorder/Functional Neurological Disorder (CD/FND), a subclassification of SSRD, found several elevated inflammation markers in FND patients, however IL-1b levels were normal (van der Feltz-Cornelis et al., 2021). This may be relevant given the finding that an IL1-b blocker was ineffective in treatment of chronic fatigue syndrome (Redlich et al., 2014). Chronic fatigue occurs often in FND, and maybe there are similarities in terms of underlying mechanism that would be relevant to the choice of anti-inflammatory medication in future research.

Finally, age and duration of illness also may play a role, especially in schizophrenia, where anti-inflammatory drugs working on vascular inflammation mostly seem to be effective in patients younger than 30. This suggests that the role of vascular inflammation may become less outspoken as a driver in long-term schizophrenia, but other inflammatory mechanisms may still be a relevant process at higher age.

4.5. Strengths and limitations

In this article we sought to only review higher level evidence, hence we selected only RCTs. Consequently, many case reports and cohort studies were excluded. These included studies assessing the role of anti-inflammatory medications in SSRD. Also, since we excluded cohorts with major somatic comorbidities, a trial establishing the psychotropic benefits of Metformin, an antidiabetic medicine, was excluded (Guo et al., 2014). Furthermore, 13 articles were excluded as authors were unable to gain full access to the text.

The included studies were highly heterogeneous in terms of their population demographics, illness stage, duration and severity, and adjunctive psychotropic medication used. They did not take comorbid mental disorders into account, which may explain some of the variation in findings.

When measuring symptomatology, a variety of different tools were used. Many studies failed to control for baseline depression or PANNS scores by not reporting the change in scores (Higgins et al., 2021). Most studies were rather small, and the studies with more participants all reported inconclusive results. However, those larger studies did not take level of inflammation into account in the analysis. Most studies did not stratify for biomarkers of inflammation at baseline.

4.6. Implications for further research

Future studies need to be targeted at patients with evidence of inflammation; however, it should be noted that peripheral inflammatory markers such as CRP can fluctuate, and are affected by confounding factors such as obesity and smoking (Yudkin et al., 1999). Future studies should also take comorbidity into account, both with somatic conditions, such as for example diabetes with comorbid depressive disorder (van der Feltz-Cornelis et al., 2021), and comorbid mental disorders, such as for example psychosis and mood disorder. This might have implications for treatment effect of a particular drug, so study participants should be well described in terms of comorbidity; if possible, selection should be done avoiding such comorbidity.

In general, higher quality studies are needed. In particular, baseline symptom scores should be controlled for in analyses by calculating change scores. Studies should specify the stage of illness (chronic vs acute) in their cohort and, if possible, augment to monotherapy only instead to a variety of TAU medications. Longer term studies are required to assess optimum treatment duration and dose, as well as the incidence of long-term adverse events.

5. Conclusion

The findings of this review suggest that there is scope to consider the use of anti-inflammatory agents in mental disorders; however, not as a one-size-fits-all solution. Treatment could be helpful in case of baseline inflammation. Anti-inflammatory medications that seem mostly effective in bipolar disorder or major depressive disorder, such as Celecoxib, Pioglitazone and statins, may differ from the ones with indications of effectiveness in schizophrenia, such as Minocycline and Aspirin. This might suggest a different underlying mechanism for treatment success in those two main illness groups. Further studies with larger sample sizes that take inflammation markers into account are needed to confirm these findings. The medications reviewed were found to be well tolerated, except, in one trial, Aspirin. Research into the possible role of anti-inflammatory medication in SSRD is at an early stage with limited evidence and requires further exploration.

Author statement

The concept for this work was developed by CFC, JS, RF and WH-C. JS and RF developed the search strategy under the supervision of CFC. Searches were run by JS and RF. All authors contributed to hand

searching. Title, abstract and full text screening was undertaken by RF and JS with discrepancies resolved through discussion with CFC. RF and WH-C completed additional full-text screening to identify studies using medications of interest for anti-inflammatory purposes. RF, JS and WH-C completed data extraction under the supervision of CFC. RF, JS and WHC contributed to early drafts of the manuscript. CFC wrote the final version of the manuscript and all authors have reviewed and edited the final manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bbih.2022.100518>.

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