Conventional Anti-Inflammatory Drugs of Major Depressive Disorder

Subjects: Neurosciences

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Major depressive disorder (MDD) is characterised by symptoms such as depressed mood, anhedonia, appetite and sleep dysfunctions, psychomotor agitation or retardation, fatigue, feelings of worthlessness, thinking or concentration problems and suicidal ideation. Its impact on health can be dramatic, as it increases the risk of cardiovascular disease, stroke, diabetes and obesity, and suicide is one of the leading causes of death, especially in the 15–29 age group. Moreover, treatment-resistant depression is an important challenge in clinical practice since 10–30% of patients are refractory to several standard antidepressant medications and have a decreased quality of life.

Keywords: depression ; anti-inflammatory ; NSAID ; cytokine inhibitor

1. Introduction

Major depressive disorder (MDD), often referred to as unipolar depression, is an important public health issue nowadays, affecting around 280 million people worldwide, which corresponds to approximately 3.8% of the population [1]. Patients with MDD experience only major depressive episodes, while patients with bipolar disorder exhibit mood fluctuations which encompass depressive episodes, known as bipolar depression in this case, and episodes of mania or hypomania [2]. MDD is characterised by symptoms such as depressed mood, anhedonia, appetite and sleep dysfunctions, psychomotor agitation or retardation, fatigue, feelings of worthlessness, thinking or concentration problems and suicidal ideation [3]. Its impact on health can be dramatic, as it increases the risk of cardiovascular disease, stroke, diabetes and obesity [4], and suicide is one of the leading causes of death, especially in the 15–29 age group [1]. Moreover, treatment-resistant depression is an important challenge in clinical practice since 10–30% of patients are refractory to several standard antidepressant medications and have a decreased quality of life [5]. Considering the various implications of this disorder, which far exceed those listed here, the constant need for developing new and efficacious therapeutic strategies seems perfectly justified.

Current medications approved for treating MDD are selective serotonin reuptake inhibitors—SSRIs, serotonin and norepinephrine reuptake inhibitors—SNRIs, tricyclic antidepressants—TCAs, monoamine oxidase inhibitors—MAOIs, N-Methyl-D- aspartate (NMDA) receptor antagonists, serotonin modulators and atypical antidepressants. They are thought to exert their actions mainly by increasing the available synaptic serotonin and/or norepinephrine [6]. This mechanism is based on the monoaminergic theory of depression, which states that a decrease in serotonin, norepinephrine and dopamine is responsible for this pathology. Chronologically, it is the first proposed theory (hence the inherent limitations of these drugs) [7]. However, with immunology as a rapidly emerging field and inflammation incriminated as an underlying cause of many diseases [8], there is growing evidence for a putative link between inflammation and depression. This finding holds promise for new possible approaches in addressing this challenging disorder [9]. Interestingly, SSRIs and SNRIs were proved to have an anti-inflammatory role in the central nervous system (CNS) which may play a part in the antidepressant effect [10].

Depression was shown to be associated with morphofunctional changes at the level of various brain areas, such as the frontal and parietal cortex, the hippocampus, the thalamus or the striatum [11]. These changes represent the substrate for the cognitive and behavioural impairments seen in this pathology. For example, striatal gray matter alterations are correlated with suicidality [12], whereas dysfunctions of the prefrontal cortex–amygdala–hippocampus circuitry possibly connected with neurovisceral structures lead to abnormal fear conditioning [13][14]. Regarding inflammatory depression, structural and functional changes in the aforementioned brain regions were identified in the context of elevated peripheral inflammatory biomarkers [15]. For instance, increased C-reactive protein (CRP) is associated with a dysfunctional corticostriatal reward circuit—a key component of treatment-resistant depression [16]. At the molecular level, neuronal impairment could be explained by the direct neurotoxic effect of inflammatory cytokines. Moreover, cytokines appear to

stimulate the tryptophan-kynurenine-quinolonic acid pathway, inducing excitotoxicity [15]. Indeed, there is increasing evidence for kynurenine pathway activation in MDD patients [17].

Mechanistic explanations for inflammation-associated depression relate to the action of cytokines on basal ganglia [18] and several polymorphisms in cytokine genes were associated with depression and response to antidepressants [19]. Sometimes, inflammatory depression is even discussed as an entirely particular subtype of depression and seems to be correlated with the prevalence of certain symptoms, such as hypersomnia, fatigue, or increased appetite. These symptoms also belong to the “atypical” subtype, which occurs in approximately 15–30% of patients [4]. Atypical depression was shown to be connected with inflammation, although some results were not consistent [20]. Of note, obesity and metabolic syndrome (inflammation-related conditions) are common findings in patients presenting with this subtype [21]. Fatigue might also be the expression of “sickness behaviour”. This energy-conserving adaptive response to infections and other inflammation-inducing situations displays similarities with depression [22]. As opposed to the atypical subtype, melancholic depression features reduced pro-inflammatory cytokines, except for exacerbations [23]. Finally, inflammation was also associated with treatment-resistant depression [24]. All these findings underline the heterogeneous nature of depression and support the need for an individualised approach to patients exhibiting different clinical pictures.

2. Conventional Anti-Inflammatory Drugs

2.1. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Perhaps some of the most used and studied anti-inflammatory treatment options are NSAIDs. They act by inhibiting the enzymes cyclooxygenase (COX)-1 and COX-2, which promote inflammatory mediators [25]. NSAIDs divide into non-selective and selective (only inhibiting COX-2). The first category includes drugs such as aspirin, diclofenac, ibuprofen, indomethacin, meloxicam, or naproxen, whereas celecoxib and etoricoxib are notable members of the second one [26].

Among non-selective NSAIDs, aspirin was shown to be a potentially successful add-on. It even decreased latency to SSRIs response in a pilot open-label study where 52.4% of the patients not previously responding to SSRI therapy showed clinically relevant improvement, mostly from the first week [27]. Moreover, treatment with aspirin was linked to a lower depression rate in the first year after a primary tumour diagnosis. This result was not achieved by other NSAIDs [28]. Unfortunately, there is only a small number of RCTs, with conflicting results. For instance, in a relatively recent study, the co-administration of aspirin and citalopram had to be interrupted, due to severe adverse reactions (anxiety, akathisia and even suicidal behaviour) (**Table 1**) [29]. However, researchers have to consider the very small number of patients included in this research and that these side effects can rather be attributed to citalopram than aspirin. While aspirin as an add-on to sertraline elicited a greater benefit than sertraline-placebo alone [30], another RCT, with escitalopram and duloxetine as concomitant medication, identified a difference only between two subgroups (i.e., duloxetine + aspirin and escitalopram + placebo). This result could also be attributed to higher baseline serum brain-derived neurotrophic factor (BDNF) in the first subgroup (**Table 1**) [31]. Two major trials from 2020 failed to show the benefit of aspirin in treating young MDD patients or preventing depression in the elderly. Berk et al. investigated the effects of rosuvastatin or aspirin in young people and found no advantage of the two over placebo. Furthermore, at week 12, aspirin was inferior to placebo in improving patients’ quality of life and to rosuvastatin on several parameters, including depression intensity [32]. Concerning a possible prophylactic effect of aspirin, the results of a multicentre, double-blinded RCT did not support a preventive role of low-dose aspirin in depression nor identify any change in depressive symptoms in participants with a history of this disease (**Table 1**) [33]. A recent meta-analysis and a systematic review attained contradictory conclusions concerning the correlation between aspirin and depression, proving the need for more extensive trials. One of them found a positive association, although infrequent, with a number needed to harm of 103 [34]. The other one demonstrated a link between aspirin and a reduced risk of developing depression [35]. To conclude, there is a clear need for further investigation, but the results are in favour of the add-on type of treatment regimen, especially in clinically depressed individuals. A summary description of the RCTs of NSAIDs in MDD can be found in **Table 1**.

In turn, naproxen was beneficial in patients with comorbid osteoarthritis and not in older healthy individuals in two randomised clinical trials, proving once again the need for a pre-existing pro-inflammatory status [36][37].

Of the selective COX-2 inhibitors, celecoxib was the most investigated as an adjunctive to antidepressants, but also in monotherapy, leading to promising results. Its effectiveness as an add-on was repeatedly proved by RCTs on patients with depression [38][39], but also with colorectal cancer [40] or with depression and comorbid brucellosis [41]. Monotherapy in patients with active osteoarthritis was also successful, similar to naproxen or ibuprofen, even if the celecoxib dose was lower than in other studies (200 versus 400 mg/day) [41]. The connection between treatment response and immunological biomarkers is supported by the correlation between interleukin (IL)-6 reduction and Hamilton Depression Rating Scale

(HAM-D) score reduction [42], together with a tendency towards higher baseline macrophage migration inhibitory factor (MIF) levels in responders [43]. On the other hand, a recent RCT failed to show any benefit of celecoxib added to vortioxetine, even when patients were stratified by high-sensitive C-reactive protein (hsCRP), but it is worthy of note that other biomarkers were not examined [44].

Various concerns are related to the use of NSAIDs in unipolar depression, as it is known that they reduce the multifunctional protein p11 levels. This protein is associated with antidepressant response and is upregulated by SSRIs by means of cytokines [18]. Thus, NSAIDs might be appropriate for enhancing treatment with TCAs or noradrenergic antidepressants, but not SSRIs [45]. Selective COX-2 inhibition promotes nitrosative and oxidative stress, decreases immunomodulator prostaglandin E2 (PGE2), and may engender psychiatric symptoms [28]. NSAIDs are also incriminated for numerous adverse effects, most notably gastrointestinal and cardiovascular [26]. However, a meta-analysis did not identify such effects associated with this particular use in depression (with limitations concerning the duration and the lack of report) [46]. It is hence argued that they might be an advantageous addition particularly in the treatment of patients at low risk of cardiovascular events, except for low-dose aspirin, which is cardioprotective [47]. Finally, a register-based study revealed that aspirin and other NSAIDs decrease the risk for early-onset depression after a first stroke episode, where inflammation is presumed to play a pivotal role. At the same time, they were associated with a high risk of depression one year after the episode, highlighting the multifaceted nature of these drugs [48]. Nonetheless, they might be considered as valuable additions to antidepressant treatment, when accounting for the patient's characteristics (clinical depression, comorbidities, inflammatory status).

Table 1. Summary of randomised controlled trials of NSAIDs in MDD.

Study	Drug and Treatment Regimen	Participants	Duration of Intervention	Immune Parameters	Main Outcomes
Ghanizadeh, 2014 [29]	Aspirin, 160 mg/day (add-on to citalopram, 20 mg/day)	10 adult out-patients with MDD	14 days; discontinued in 8 out of 10 patients	Not measured	Harmful
Zdanowicz, 2017 [31]	Aspirin, 100 mg/day (add-on to escitalopram or duloxetine)	40 individuals with MDD	2 years	Not measured	Not effective (but duloxetine + aspirin superior to escitalopram + placebo)
Sepehrmanesh, 2017 [30]	Aspirin, 2 × 80 mg/day (add-on to sertraline, 50–200 mg/day)	100 patients with MDD	8 weeks	Not measured	Effective
Berk, 2020 (YoDA-A) [32]	Aspirin, 100 mg/day or rosuvastatin 10 mg/day (add-on to treatment as usual)	130 young people (15–25 years) with moderate to severe MDD	12 weeks	Not measured	Not effective
Müller, 2006 [38]	Celecoxib, 400 mg/day (add-on to reboxetine 4–10 mg/day)	40 patients with MDD	6 weeks	Not measured	Effective as add-on
Akhondzadeh, 2009 [39]	Celecoxib, 2 × 200 mg/day (add-on to fluoxetine 40 mg/day)	40 adults with MDD	6 weeks	Not measured	Effective as add-on
Musil, 2011 [49]	Celecoxib, 400 mg/day (add-on to reboxetine 4–10 mg/day)	32 patients with MDD and 20 healthy controls	6 weeks	No difference in MIF, TGF-β and sCD14	Effective as add-on
Abbasi, 2012 [42]	Celecoxib, 2 × 200 mg/day (add-on to sertraline 200 mg/day)	40 patients with MDD	6 weeks	Reduced IL-6	Effective as add-on

Study	Drug and Treatment Regimen	Participants	Duration of Intervention	Immune Parameters	Main Outcomes
Majd, 2015 [50]	Celecoxib, 2 × 100 mg/day (add-on to sertraline, 25, then 50 mg/day)	30 women with MDD (first episode), 18–50 years old	8 weeks	Not measured	Effective after 4 weeks, not significant after 8 weeks
Alamdarsaravi, 2017 [40]	Celecoxib, 400 mg/day (monotherapy)	40 patients with mild to moderate MDD and colorectal cancer	6 weeks	Not measured	Effective
Krause, 2017 [51]	Celecoxib, 400 mg/day (add-on to reboxetine, 4–10 mg/day)	40 patients with MDD and healthy controls	6 weeks	Not measured	Remission in celecoxib group predicted by higher KYN/TRP baseline ratio
Baune, 2021 [44]	Celecoxib, 400 mg/day (add-on to vortioxetine 5–10 mg/day)	119 patients with MDD	6 weeks	Participants were stratified by hsCRP (> or ≤3 mg/L)	Not effective
Simon, 2021 [43]	Celecoxib, 2 × 200 mg/day (add-on to sertraline, 50–150 mg/day)	43 patients with MDD, 18–60 years old	6 weeks	MIF: lower at baseline in placebo remitters than non-remitters, trend for higher baseline levels in celecoxib responders than non-responders; neopterin, TNF-α: no clear pattern	Not effective
Mohammadinejad, 2015 [52]	Celecoxib, 2 × 200 mg/day or diclofenac, 2 × 50 mg/day (monotherapy)	52 patients with MDD and breast cancer	6 weeks	Not measured	Celecoxib more effective than diclofenac

MDD, major depression disorder; MIF, macrophage migration inhibitory factor; TGF-β, Transforming growth factor-β; sCD14, soluble CD14; IL, interleukin; TNF-α, tumour necrosis factor-alpha; KYN, kynurenine; TRP, tryptophan; hsCRP, high-sensitive C reactive protein.

2.2. Cytokine Inhibitors

As NSAIDs are often thought to be too “off-target”, cytokine inhibitors, which have a history of inflammatory conditions treatment, may be more suitable for the purpose under discussion. Indeed, they have been studied and proved effective, especially in the presence of such comorbidities [53][54]. A problem that arises is that it is not always clear if the reduction in depressive symptoms is direct or indirect, due to a change in the primary disease’s characteristics. For example, in a study on patients with hidradenitis suppurativa, adalimumab led to a greater improvement in participants with higher baseline pain [55].

Supporting the theory of a separate depression subtype, they were most effective when plasma cytokine levels were increased. For instance, infliximab—a TNF antagonist, surpassed placebo in depression score reduction only in the hsCRP > 5 mg/L group. This effect was enhanced by high baseline TNF together with its soluble receptors. In contrast, placebo was superior in the baseline hsCRP ≤ 5 mg/L group [18]. Conversely, another RCT of infliximab reported an improvement in depressive symptoms which was no longer significant after eliminating the influence of ankylosing spondylitis disease activity and did not correlate with CRP levels [53]. Adalimumab and etanercept, other TNF-α antagonists, improved depression scores in patients with rheumatic (i.e., ankylosing spondylitis), Crohn’s disease, psoriasis or hidradenitis suppurativa and comorbid depressive symptoms [54][55][56][57][58]. Dupilumab, an antagonist of the receptor of IL-4, showed similar results to those of the anti-TNF-α monoclonal antibodies concerning antidepressant efficacy [59][60][61]. A summary description of the RCTs of cytokine inhibitors in patients with MDD or with depressive symptoms and comorbid medical condition can be found in **Table 2**.

Several less common drugs target specific cytokines whose exact role in depression is not known, but which seem to be, sometimes, even more effective. Such is the case of ixekizumab, an IL-17A inhibitor which, according to data from a recent RCT, improved depressive symptoms in patients with psoriasis, whereas TNF-α inhibitor etanercept did not,

suggesting a particular role of IL-17A in the CNS [62]. Another example, guselkumab, an IL-23 inhibitor, was investigated in psoriasis patients and was proved superior to adalimumab, maintaining its outcome on depression even after adjustment for the effects related to disease activity [63].

There remains the threat of potentially serious side effects, such as infections, which were not identified by the previously mentioned meta-analysis conducted by Köhler et al. [46], although in the context of a small number of studies. As outlined by the existing data, cytokine inhibitors possess a more targeted effect on depression-related inflammation than those previously discussed and show some promise in alleviating depressive symptoms in specific groups, i.e., patients with pre-existing inflammatory comorbidities, but more research is needed to reveal the exact effect in MDD without comorbid medical conditions.

Table 2. Summary of randomised controlled trials of cytokine inhibitors in patients with MDD or with depressive symptoms and comorbid medical condition.

Study	Drug and Treatment Regimen	Participants	Duration of Intervention	Immune Parameters	Main Outcomes
Raison, 2013 [18]	Infliximab (3 infusions of 5 mg/kg at baseline and weeks 2 and 6) (monotherapy or add-on to treatment as usual)	60 patients with treatment-resistant MDD	12 weeks	Greater decrease in hsCRP in responders	More effective when baseline hsCRP > 5 mg/dL
Webers, 2020 [53]	Infliximab (infusions of 5 mg/kg infliximab or placebo at weeks 0, 2, 6, 12, and 18; from week 24 until week 54, all patients received infliximab therapy)	23 patients with ankylosing spondylitis	54 weeks	CRP levels not related to depression	Effective in improving symptoms
Loftus, 2008 [57]	Adalimumab, Induction: open-label adalimumab 80-mg, then a 40-mg dose at week 2; then adalimumab 40 mg weekly/every other week or placebo injections	499 patients with Crohn's disease	56 weeks	Not measured	Effective; no difference between adalimumab weekly/every other week for all visits
Menter, 2010 [58]	Adalimumab, 40 mg every other week	96 patients with psoriasis	12 weeks	Not measured	Effective
Scheinfeld, 2016 [55]	Adalimumab, 40 mg weekly/every other week	154 patients with hidradenitis suppurativa	16 weeks	Not measured	Effective in patients with high baseline pain
Simpson, 2016 [59]	Dupilumab, 100 mg every 4 weeks/200 mg every 2 weeks/300 mg every 2 weeks/300 mg QW	380 adults with moderate to severe atopic dermatitis	16 weeks	Not measured	Effective (300 mg weekly/every 2 weeks)
de Bruin-Weller, 2018 [60]	Dupilumab, 300 mg weekly/every 2 weeks + topical corticosteroids	318 adults with atopic dermatitis	16 weeks	Not measured	Effective
Cork, 2020(SOLO 1 and 2) [61]	Dupilumab, 300 mg weekly/every 2 weeks	1379 patients with atopic dermatitis for ≥ 3 years	16 weeks	Not measured	Effective
Tyring, 2006 [54]	Etanercept, 50 mg BIW	618 patients with psoriasis	12 weeks	Not measured	Effective
Tyring, 2013 [56]	Etanercept; Group A: etanercept 50 mg BIW for 12 weeks, followed by etanercept 50 mg QW and placebo QW for 12 weeks. Group B: placebo BIW for 12 weeks, followed by etanercept 50 mg BIW for 12 weeks.	121 patients with moderate-to-severe plaque psoriasis with scalp involvement	24 weeks	Not measured	Effective

Study	Drug and Treatment Regimen	Participants	Duration of Intervention	Immune Parameters	Main Outcomes
Langley, 2010 [64]	Ustekinumab, 45 or 90 mg at weeks 0, 4, and every 12 weeks through week 52, or placebo at weeks 0 and 4 + 45 or 90 mg of ustekinumab at weeks 12, 16, and every 12 weeks	1230 patients with psoriasis	Results reported through 24 weeks	Not measured	Effective
Griffiths, 2017 [62]	Ixekizumab, 80 mg every 2/4 weeks, initial dose 160 mg; etanercept, 50 mg BIW	575 patients with psoriasis	12 weeks	Reduction in hsCRP	Ixekizumab effective
Gordon, 2018 [63]	Guselkumab, 100 mg at weeks 0, 4, 12, and 20; placebo at weeks 0, 4, 12 followed by guselkumab 100 mg at weeks 16, 20; or adalimumab, 80 mg at week 0, 40 mg at week 1, and 40 mg every-2-weeks through week 23	989 patients with psoriasis	24 weeks	Not measured	Guselkumab more effective

hsCRP, high sensitive C reactive protein; MDD, major depressive disorder; CRP, C reactive protein; BIW, twice weekly; QW, once weekly.

2.3. Corticosteroids

Other powerful anti-inflammatory drugs, corticosteroids, have generated positive results in unipolar depression, but their serious side effects represent an important disadvantage [47]. Moreover, there is a putative correlation between this type of medication and atypical depressive syndromes [65].

Regarding evidence in favour of an antidepressant role of corticosteroids, a 4-day course of treatment with dexamethasone in MDD patients was superior to placebo, based on HAM-D scores 14 days after the beginning of the intervention [66]. In turn, hydrocortisone produced an acute antidepressant effect compared to placebo and corticotropin-releasing hormone (CRH) in a double-blind, placebo-controlled study [67]. However, data from an RCT on cardiac surgery patients (n = 1244) revealed that a single intraoperative intravenous dose of dexamethasone does not impact depression, except for the female subgroup, which might be more affected by hypothalamic-pituitary-adrenal axis dysfunctions [68]. Moreover, in men with chronic pelvic pain syndrome, one month of treatment with oral prednisolone only led to a trend towards improving depression (quantified by Hospital Anxiety and Depression Scale), in the context of normal baseline values for these scores [69]. In patients with cancer-related fatigue, dexamethasone improved quality of life but did not exert an antidepressant effect [70].

Eventually, the results of a network meta-analysis imply that corticosteroids have a greater antidepressant capacity than other anti-inflammatory agents, but the head-to-head comparisons identified no statistically significant difference between these classes [71].

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