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Efetividade dos AINEs no tratamento da depressão major: uma revisão compreensiva / Effectiveness of NSAIDs in the treatment of major depressive disorder: a comprehensive review

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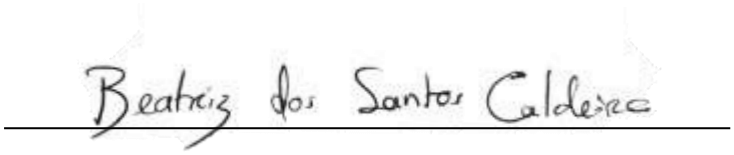

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Effectiveness of NSAIDs in the treatment of major depressive disorder: a comprehensive review

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Effectiveness of NSAIDs in the treatment of Major Depressive Disorder: A Comprehensive Review

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Abstract

Background/Objectives: The inflammatory hypothesis in the aetiology of depression raised the opportunity for new therapeutic tools as first line, adjunctive or symptomatic treatment of Major Depressive Disorder (MDD). Studies assessing the efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) have yielded inconsistent results. The present review provides an updated overview of such studies with the aim of clarifying the effectiveness of NSAIDs as therapeutic strategies in patients with MDD.

Methods: A literature search was conducted to retrieve clinical trials using NSAIDs for the treatment of MDD. Besides the completed randomised and controlled clinical trials (RCTs), non-randomised and non-placebo-controlled trials were also included in the search (non-RCTs). Studies with NSAIDs as monotherapy and/or as adjunct of antidepressant therapies, across all age groups were included to tentatively strengthen the qualitative assessment of NSAID effectiveness. Relevant articles, published prior to January 2020 were retrieved by querying eight databases, namely PubMed, Google Scholar, PubMed Central, Web of Science, JAMA Psychiatry, ClinicalTrials.gov, Cochrane Central Register of Controlled Trials and ICTRP. Additional articles were manually scrutinized from bibliography listings of the selected articles.

Results: Fourteen records, comprising 15 clinical studies, were identified for inclusion in the qualitative synthesis. Seven RCTs investigated the efficacy of NSAIDs in a total of 2758 patients. Six of these demonstrated a significantly positive effect when used as adjunctive treatment, and one demonstrated no effect as monotherapy. Among the eight non-RCTs, five analysed the effect of adjunctive NSAIDs treatment on the depressive symptoms of 130 277 patients, from which two revealed a significantly negative effect and three showed no effect. The other three non-RCTs, conducted on a total of 20 865 non-depressed participants, failed to confirm the preventive effect of NSAIDs. Internal and external validity is compromised by the majority of the study designs. In particular, most RCTs had small sample sizes and short follow-up durations. Additionally, the studies were heterogeneous in terms of exposure and outcome assessments, therapeutic schemes as to drug combinations and dosage, as well as covariates applied for result adjustments.

Conclusions: Overall, NSAIDs may exert a beneficial therapeutic effect in MDD as an adjunctive treatment to antidepressants, although methodological heterogeneity introduces some inconsistencies. NSAIDs appear to have no effect as a preventive measure in MDD, particularly amongst the elderly. Study designs need to address the highly heterogeneous pathophysiology and presentation of MDD by deep phenotyping, and by targeting specific inflammatory

mechanisms. Selective patient recruitment for uniformity, together with well-matched controls, can provide statistically powerful and clinically meaningful data. Genotypic profiling would ultimately contribute towards a better understanding of the role of inflammation, and anti-inflammatory drugs, in MDD.

Keywords: Major depressive disorder, depression, nonsteroidal anti-inflammatory drugs, inflammation, clinical trials

1. Introduction

According to the World Health Organization (WHO), depression is a leading cause of disability and a major contributor to the overall global burden of disease (https://www.who.int/news-room/fact-sheets/; updated 30 January 2020). Its rising tendency has long concerned WHO authorities, culminating in a resolution that was passed in May 2013 by the World Health Assembly (WHA) – the *Comprehensive Mental Health Action Plan 2013–2020* (http://www.who.int/mental_health/action_plan_2013/en/).

Major depressive disorder (MDD), with typical symptoms of depressive mood, anhedonia and lack of interest, is the leading contributor to disability by depression; it is said to affect approximately 6% of adults worldwide every year and it is expected to be the leading cause of disease burden by 2030 [1] [2] [3]. Besides its direct toll in the form of decreased quality of life, the disorder carries burdens related to mortality (suicide and cardio- and cerebrovascular risks), functional impairment (psychosocial interaction and productivity/labour capacity) as well as those that extend to family-related and economic issues [3].

A wide variety of pharmacological antidepressants have been available for some time, but they are often ineffective. Evidence from large trials with various drugs show that around 30% of patients do not experience remission; even treatment-responsive patients have high relapse and recurrence rates, and overall cumulative remission rate is only around 67% after four acute treatment steps, with relapse rates increasing as more treatment steps are required [4]. The fact that depression remains largely refractory to these drugs has demanded the continued search for alternative treatment strategies.

Historically the monoamine deficiency hypothesis has stood its ground in the pathophysiology underlying depression [5], but it is now also well established that there is a link between depression and inflammatory factors within the innate and the adaptive immune system [6] [7]. An overview of some of these interacting mechanisms is represented in Figure 1.

The central nervous system (CNS) integrates the body's inflammatory response in a process designated neuroinflammation [7]. Cytokines and other inflammatory mediators, which establish the communication between the CNS and the peripheral environment, either bind to receptors of nerve fibres, are actively transported or directly cross the leaky regions in the blood-brain barrier [8]. Cells lining the vasculature, as well as the endothelium itself, may also be inflammation intermediaries [8]. In the CNS, these inflammatory signals activate the microglia (their primary cellular recipient), which go from an immuno-surveillance to a reactive macrophage-like state [7] [8]. Evidence of such activation includes increased levels of

translocator protein (TSPO) found on the external mitochondrial membranes [9]. Interestingly, this increase has been observed during major depressive episodes secondary to MDD, and appears to correlate with the Hamilton Depression Rating Scale (HAM-D) score [9].

Abnormally activated microglial cells release pro-inflammatory cytokines, namely interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β) [10] [11] [12], and preferentially type-1 cytokines such as interleukin-12 (IL-12) [12]. MDD patients also present increased levels of other pro-inflammatory cytokines, particularly interleukin-2 (IL-2) and interferon-γ (IFN-γ) by activated T-cells [12] [13], macrophage migration inhibitory factor (MIF) [14], neopterin (a type-1 cellular response sensitive marker) and positive acute phase proteins [12]. Since interleukin-4 (IL-4) is a central type-2 cytokine, the elevated IFN-γ/IL-4 ratio found in depressed patients supports this type 1/type 2 immune response imbalance [12].

These central inflammatory molecules act on various fronts. One such instance is down the prostaglandin biosynthetic cascade, initiated by prostaglandin-endoperoxide synthase (PTGS), more commonly known as cyclooxygenase (COX) [8]. COX-1 is constitutively expressed whereas COX-2 is mostly expressed during inflammation, although some findings indicate that the latter may have a constitutive function in the brain [14]. Among other end-products, prostaglandin E2 (PGE2) is synthesised through this cascade and its increased levels have been registered in saliva, cerebrospinal fluid and serum of patients with MDD [15].

In another pathway, these inflammatory mediators increase the number and activity of presynaptic monoamine reuptake pumps, via a mitogen-activated protein kinase (MAPK)-mediated process, thereby decreasing the synaptic availability of norepinephrine, dopamine and serotonin [7].

The pro-inflammatory cytokines, together with PGE2, also stimulate the hypothalamic–pituitary–adrenal (HPA) axis and decrease the expression and sensitivity of glucocorticoid receptors [8] [15] [16], leading to high levels of circulating stress hormone cortisol [8] [12] [16]. Cortisol, in turn, enhances microglia activation and proliferation [12] and is associated with reduced synaptic number and function [17] as well as reduced hippocampal volume [18].

In the tryptophan metabolic pathway, pro-inflammatory mediators and cortisol all stimulate the activity of specific enzymes along the kynurenine pathway [7] [8] [12] [19] [20], diverting its metabolism from the serotonin pathway. This may lead to serotonin deficiency, as tryptophan availability is the limiting step of this monoamine synthesis [12]. Also consequent to the cytokine-mediated enzyme activation, kynurenine is preferentially metabolized to quinolinic acid, rather than kynurenic acid, which is considered a N-methyl-D-aspartate

receptor (NMDA-R) antagonist and a neuroprotective metabolite [21]. Indeed, a higher kynurenine/kynurenic acid ratio is associated with more pronounced depressive symptoms [12].

Kynurenine metabolism occurs mainly in macrophages, microglial cells and astrocytes. However, as astrocytes do not express kynurenine monooxygenase (KMO), they become the prime source of kynurenic acid in the CNS. The astrocytic/microglial activation imbalance therefore contributes to the increased quinolinic acid production [12].

In turn, quinolinic acid - a strong NMDA-R agonist [19] that acts as a neuro- and gliotoxin - promotes an increased glutamate release in the striatum and the cortex [12]. Simultaneously, astrocyte loss and/or lowered responsiveness, with consequent reduction in their glutamate reuptake [12], prolongs the synaptic activation of glutamate. The excessive levels of extra-synaptic glutamate result in neuronal excitotoxicity [21] and decreased synthesis of brain-derived neurotrophic factor (BDNF) – the neurotrophin that promotes neuronal survival, integrity and plasticity [7] [8] [22].

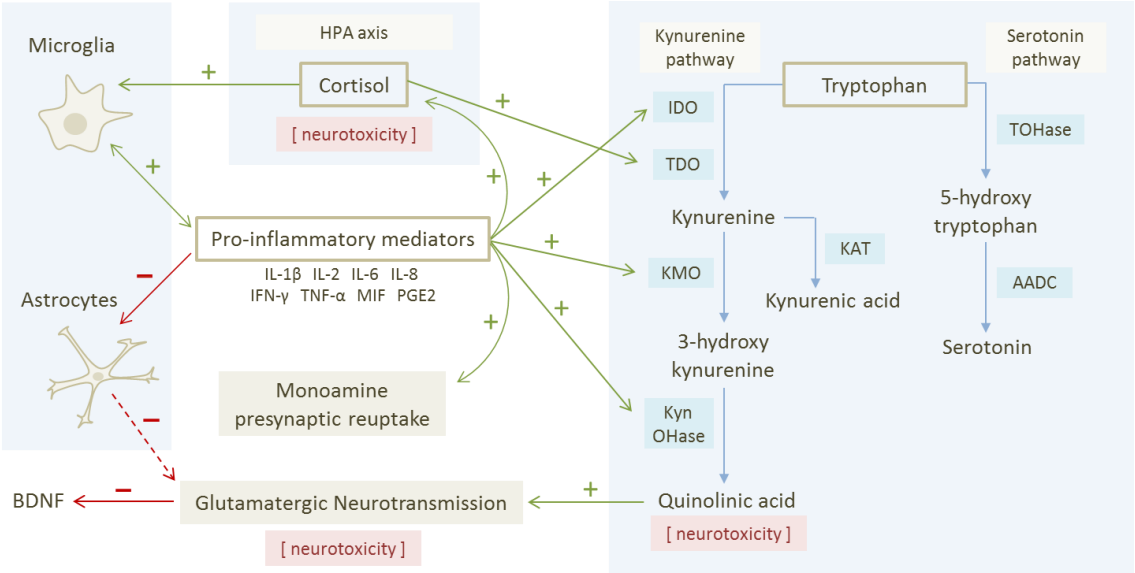

Figure 1: Schematic representation of the role of some inflammatory mechanisms in the pathophysiology of MDD.

Focus on central inflammatory mediators, showing their direct or indirect influence on glial cells, HPA axis, tryptophan metabolism, and the combined effect on glutamatergic neurotransmission. As an end result, normal neuronal function is compromised.
HPA: hypothalamic pituitary adrenal; IL: interleukin; IFN-γ: interferon-γ; TNF-α: tumor necrosis factor α; MIF: macrophage migration inhibitory factor; PGE2: prostaglandin E2; BDNF: brain-derived neurotrophic factor; IDO: indoleamine 2,3-dioxygenase; TDO: tryptophan 2,3-dioxygenase; KAT: kynurenine aminotransferase; KMO: kynurenine monooxygenase; KynOHase: kynurenine hydroxylase; TOHase: tryptophan hydroxylase; AADC: aromatic L-amino acid decarboxylase. Arrows with +/– indicate positive/negative effect; dashed arrow illustrates diminished negative effect of astrocytes (consequent to the influence of pro-inflammatory mediators); filled arrowheads describe metabolic pathways.

The neurological consequences of neuroinflammation in MDD patients, particularly the hippocampal atrophy, have been well demonstrated by *post mortem* studies as well as *in vivo* imaging techniques [8] [12] [18].

Numerous clinical trials have been carried out that aim to evaluate the efficacy of anti-inflammatory treatment strategies in MDD, or in depression as a whole. Systematic reviews and meta-analyses of these studies have yielded contradictory results concerning their efficacy, and have also highlighted the limitations regarding study designs.

Here, we provide an updated review of published clinical studies investigating the efficacy of NSAIDs in particular, when used as monotherapy or as an adjunct to antidepressant drug therapy in the treatment of MDD.

2. Methods

2.1 Search methods

The present comprehensive review was carried out in accordance with the PRISMA (*preferred reporting items of systematic reviews and meta-analyses*) guidelines. Searches were conducted in the English language, from inception to January 2020.

The following eight databases were queried with the respective strings or keywords, as well as the respective filters where indicated:

- PubMed and Google Scholar: (NSAID[Title/Abstract] OR NSAI[Title/Abstract] OR Anti-Inflammatory Agents, Non-Steroidal[MeSH Terms]) AND (MDD[Title/Abstract] OR Depressive Disorder, Major[MeSH Terms])
- PubMed Central, Web of Science and JAMA Psychiatry: (NSAID OR NSAI OR Anti-Inflammatory Agents, Non-Steroidal) AND (MDD OR Depressive Disorder, Major)
- ClinicalTrials.gov: Keywords: "Major depressive disorder" OR "MDD" AND "NSAID" – limited to Titles and Abstracts. Filters applied: Completed + Interventional (clinical trial) + with results
- *Cochrane Central Register of Controlled Trials:* Keywords: NSAIDs; Major Depressive Disorder; MDD; major depression – limited to Titles and Abstracts.
- ICTRP: Keywords: Major depressive disorder OR MDD OR major depression AND NSAID OR non-steroid anti-inflammatory agent. Filters applied: Major depressive disorder OR MDD OR major depression AND random AND controlled (title) + Major depressive disorder with synonyms (condition) + Phase 4 (recruiting status) + with results only (description) + with results.

Article selection was according to the criteria described below, and additional literature was retrieved by manual scrutiny of bibliography listings of selected articles, whenever this was considered relevant for inclusion or necessary for data evaluation.

2.2 Eligibility

Studies eligible for this review were those that met the following criteria:

- Individuals diagnosed with major depressive disorder (MDD), as ascertained by rating scales such as HDRS/HAM-D (Hamilton Depression Rating Scale), MADRS (Montgomery-Åsberg Depression Rating Scale), ICD-9 (International Classification of Disease, 9th Edition) or others, as well as SCID (Structured Clinical Interview for Depression) with or without previous self-

rating in self-report questionnaires. No restrictions were placed regarding episodic or long-standing MDD, neither were there limitations as to participant age ranges.

- The use of NSAIDs, prescribed as monotherapy or as an adjunct to antidepressant drug therapy. History of NSAID usage (medical records or self-reported) was included. No restrictions were placed on the antidepressants used.
- Retrospective or prospective studies examining the influence of NSAIDs on depression onset/incidence.
- In order to obtain a comprehensive overview, both randomised, placebo-controlled clinical trials (RCTs) and non-randomised, non-placebo-controlled trials were included.

2.3 Exclusion criteria

Studies were excluded based on at least one of the following criteria:

- Non-human studies.
- Studies involving depressive disorders other than MDD, or where MDD had not been analysed as a separate group (for example in general "depression" in cohorts).
- Not using NSAIDs, or joint analysis of NSAIDs plus other anti-inflammatory agents (for example NSAIDs plus statins, simultaneously).
- Participants with inflammation that could be attributable to other, major co-morbid conditions (risk of influencing trial outcomes).
- Inadequate study design (analysis of side effects, other reasons).
- Studies published only as abstracts from conference proceedings, with incomplete data as required for the present review.

2.4 Data extraction

The records deemed eligible for this review were advanced to full-text reading with detailed data inspection.

A data extraction template was designed to aid annotation of all relevant information from each article. Besides the bibliographic identification of the study, extracted data included the study design (type of clinical trial, sample size, duration), the population characteristics (gender, age groups, co-morbidities), the treatment(s), the assessment of depression (diagnostic criteria, outcome measures, response criteria), the assessment of inflammation (baseline, post-treatment) and the observed results.

3. Results

3.1 Search results

Search results are outlined in Figure1. A total of 702 records were retrieved from the different databases, with the following breakdown: PubMed – 45; PMC – 89; Web of Science – 12; JAMA – 6; ClinicalTrials.gov – 490; *Cochrane Central Register of Controlled Trials – 27;* ICTRP – 33.

After removing 33 duplicates, the abstracts of the remaining 669 retrievals were screened for eligibility according to the predetermined inclusion criteria, resulting in 49 papers selected for full-text screening. A total of 38 records were excluded. Reasons for exclusion are summarized in Figure 1. The studies excluded on the basis of major co-morbidities (considered to influence trial outcomes), involved participants with conditions such as Rett syndrome, pulmonary fibrosis, cancer, active osteoarthritis or stroke. The most frequent exclusion criterion was inadequacy of study design. Amongst these were: a study protocol in itself, single case reports including one on drug use disorder, a non-interventional assessment of post-partum depression, assessment of how expectancy influences outcome in a randomized controlled trial, and several studies assessing side-effects only.

During the full-text screen of the 49 records, one was found to be an Abstract of work presented at a scientific meeting; however, this was included because it contained the information considered adequate for analysis. Also, from these full-text screens, a further 3 relevant papers were identified by manual inspection of the bibliographical listings. A total of 14 records were thus considered to meet the criteria. As one of these records comprised two eligible trials, a total of 15 studies were elected for the present qualitative review.

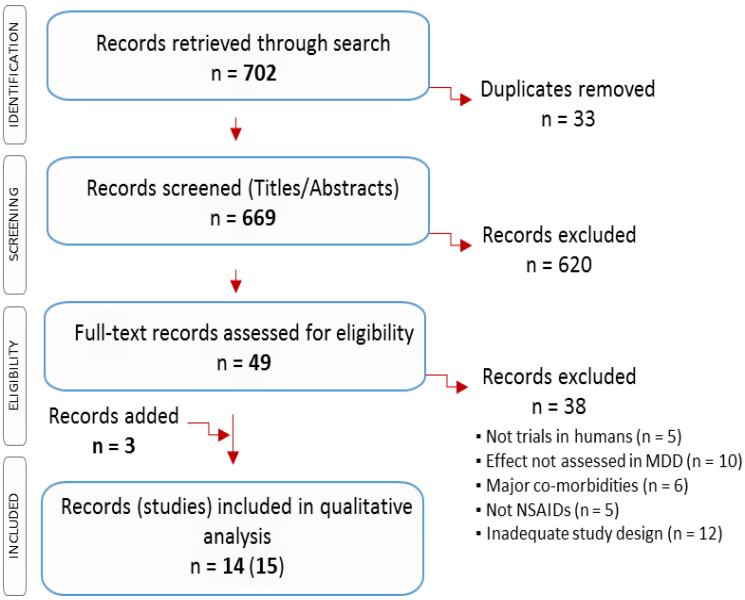

Figure 2: Flow diagram of PRISMA record retrieval and selection for the present review.

3.2 Study characteristics

The extracted data from elected studies were annotated in a single predesigned template. Given the heterogeneity of the studies, and in order to enable a critical analysis, these were divided into two study-types: RCTs and non-RCTs (including a partially randomised trial), the latter further subdivided according to depressed versus non-depressed study cohorts. Relevant data from each study-type are shown in Table 1 (RCTs) and Table 2 (non-RCTs).

3.2.1 RCTs

There were a total of seven RCTs exploring the efficacy of NSAIDs on depressive symptoms (n=2 758), six of which with NSAIDs as an adjunct to antidepressant drug therapy and one where these had been prescribed as monotherapy.

A significant positive effect of NSAIDs, compared to placebo, was found by all six RCTs with NSAIDs as adjunctive treatment (n=230), whereas the remaining RCT found no significant effect of NSAID monotherapy, compared to placebo (n=2 528).

Inflammatory biological markers were assessed in three RCTs with adjunctive NSAID therapy (n=120), although each study analysed different molecules. Musil *et al*. (2011) documented significantly higher levels of MIF and lower levels of TGF-β at baseline in depressed patients, but neither appeared to be associated with HAM-D-17 scores. No difference in sCD14 serum levels was noticed between patients and controls [14]. Abbasi *et al*. (2012), however, demonstrated that celecoxib was capable of reducing IL-6 serum levels, and that this correlated with HAM-D-17 scores [23]. Finally, Zdanowicz *et al*. (2017) showed that in patients treated with ASA and duloxetine, those who showed a quicker symptomatic improvement and a higher remission rate presented higher BDNF levels compared to patients taking placebo and escitalopram [24].

Heterogeneity was evident in terms of therapeutic scheme, outcome definition and, to a minor extent, age range. The most studied drug combination consisted of celecoxib and a selective serotoninergic reuptake inhibitor (SSRI). The most used tool for MDD diagnosis was DSM-IV and the most frequent outcome measure was defined by the HAM-D-17 score, although response criteria cut-off values varied substantially. There was minor variability concerning participants' age, with studies electing people preferably under 50 years of age.

TABLE 1: Study characteristics of identified RCTs.

Study					Population Characteristics		Treatment	Depression Assessment			Inflammation Assessment	Results
Source	Design (RCT)	Duration	Sample Size		% Male (Treatment / Control)	Age (years) (Treatment / Control)		Diagnostic Criteria	Outcome measure	Response Criteria		
			Randomized (Treatment)	Analyzed (Treatment)								
Muller (2006)	Double-blind, placebo; parallel-group pilot study; double-centered	6 weeks	40 (20)	40 (20)	50 (60 / 40)	Range 23-65, mean 44.4 (mean 44.6 ± 11.6 / mean 44.3 ± 13.5)	celecoxib (400 mg id) + reboxetine (4-10 mg id) or placebo + reboxetine (4-10 mg id) Comedication: Lorazepam allowed for acute agitation/anxiety	DSM-IV (Single episode 296.2 or Recurrent 296.3)	HAM-D-17 weekly	≥ 30% HAM-D-17 score reduction defined response, HAM-D-17 ≤ 7 at week 6 in the intent-to-treat groups defined remission	Not assessed	HAM-D-17 scores decreased in both treatment groups (p<0.0001; S), but celecoxib group showed greater scores reduction vs. placebo group (p=0.035; S). Response rate was higher in the celecoxib group vs. placebo group (57% and 45%, respectively, p≤0.053); NS Remission rate was higher in the celecoxib group vs. placebo group (45% and 20%, respectively, p≤0.088); NS No statistical significant difference could be observed between both groups regarding the plasma levels of reboxetine or the use of benzodiazepines.
Akhondzadeh (2009)	Double-blind, placebo; prospective parallel-group trial; multicentered	6 weeks	40 (20)	37 (19)	37.5 (35 / 40)	Range: 24-46 (mean 34.7 ± 6.8 / mean 34.2 ± 5.0)	celecoxib (200 mg bid) + fluoxetine (40 mg id) or placebo + fluoxetine (40 mg id)	DSM-IV-TR, HAM-D-17 ≥ 18 and item 1 of HAM-D ≥ 2	HAM-D-17	≥ 50% HAM-D-17 score reduction defined response. Endpoint HAM-D-17 ≤ 7 defined remission	Not assessed	From baseline to endpoint, HAM-D-17 scores changed in both groups, p=0.02; S Effect of fluoxetine plus celecoxib on endpoint HAM-D-17 vs. fluoxetine plus placebo, p=0.001; S Response rate 90%; S Remission rate 35%; S
Musil (2011)	Double-blind, placebo; prospective parallel-group trial	6 weeks	Depressed patients: 40 Healthy controls: 20	Depressed patients: 32 (18) Healthy controls: 20	Depressed patients: 50.0 (celecoxib group 61.1 / placebo group 35.7). Healthy controls: 75	Depressed patients: range 23-65, mean 44.6 ± 11.6 (celecoxib group mean 44.8 ± 12.2 / placebo group mean 44.3 ± 11.1). Healthy controls: range 24–60, mean 40.0 ± 10.4	celecoxib (400 mg id) + reboxetine (4-10 mg id) or placebo + reboxetine (4-10 mg id) or healthy control group without medication. Comedication: Lorazepam allowed for acute agitation/anxiety	DSM-IV (Single Episode 296.2x or Recurrent 296.3x)	HAM-D-17 weekly	≥ 30% HAM-D-17 score reduction over the observation period of 5 weeks defined response. HAM-D-17 ≤ 7 after 5 weeks in the intent-to-treat group defined remission	MIF, sCD14 and TGF-β serum levels measured at baseline, week 3 and week 5 (ELISA)	Effect of celecoxib on HAM-D-17 vs. placebo, p=0.028; S Elevated MIF levels at baseline vs. healthy controls, p<0.001; S Higher MIF levels in male controls vs. female controls, p=0.021; S Decreased TGF-β levels at baseline vs. healthy controls, p=0.006; S No difference of sCD14 levels at any time. No associations between HAM-D-17 scores and the immune parameters.
Fields (2012)	Double-blind, placebo; from ADAPT cohort; multicentered	0-60 months; median >2 years	2 528 (ND)	2 312 (ND)	54.1 (celecoxib group: 52.9; naproxen sodium group: 54.1 / placebo group: 54.9)	Range 70-90, median 74.5 (celecoxib group: range 70-91, median 74.5; naproxen group: range 70-89, median 74.5 / range 70-91, median 74.4)	celecoxib (200 mg bid) or naproxen sodium (220 mg bid) or placebo	0 CAB included GDS-30 and 3MS-E. GDS-30 score > 5 defined depression (corresponding to approximately one-fifth of cohort (± 506)).	CAB yearly	Same as outcome measure	Not assessed	Over time, mean GDS-30 scores increased slightly in all 3 treatment groups; NS In multivariable modeling, there was no effect of either treatment on follow-up GDS-30 scores vs. placebo group (celecoxib group: p=0,34; naproxen group: p=0,42); NS Higher baseline GDS-30 scores, a prior psychiatric history, older age, time in the study, and lower cognition interacting with time were all associated with higher follow-up GDS-30 scores (p<0.01); S
Abbasi (2012)	Double-blind, placebo; parallel-group trial; double-centered	6 weeks	40 (20)	37 (19)	67.5 (65 / 70)	Range 18-50 (mean 35.1 ± 8.0 / mean 34.2 ± 6.9)	celecoxib (200 mg bid) + sertraline (200 mg id) or placebo + sertraline (200 mg id)	DSM-IV-TR, HAM-D-17 ≥ 18 and item 1 of HAM-D ≥ 2	HAM-D-17	≥ 50% HAM-D-17 score reduction defined response, HAM-D-17 ≤ 7 defined remission	IL-6 serum levels measured at baseline and week 6 (Sandwish Enzyme Immunoassay)	ES 0,68 to 0,95; S Response rate 95%; S Remission rate 35%; S Serum IL-6 levels (baseline, week 6) correlation to HAM-D-17 (r=0.378, r=0.673); S

(continued)

TABLE 1: Study characteristics of identified RCTs (continued).

Majd (2015)	Double-blind, placebo; parallel-group trial; double-centered	8 weeks	30 (15)	23 (14)	0	Eligibility range 18-50 (mean 34.8 ± 7.3 / mean 36.2 ± 12.7)	celecoxib (100 mg bid) + sertraline (50-100 mg id) or placebo bid + sertraline 50-100 mg id (25 mg during first 3 days)	SCID; HAM-D-17 score between 18-36	HAM-D-17 (primary outcome); HAM-A (secondary outcome) at week 4 and 8	≥ 50% HAM-D-17 score reduction at week 4 or 8 defined response, HAM-D-17 ≤ 7 at week 8 defined remission	Not assessed	In both treatment groups, HAM-D-17 and HAM-A scores decreased from baseline to week 4, but celecoxib group showed greater scores reduction vs. placebo group (p=0.021 and p=0.05, respectively); S In both treatment groups, HAM-D-17 and HAM-A scores decreased from baseline to week 8, but celecoxib group showed greater scores reduction vs. placebo group; NS Response rate at week 4 was higher in the celecoxib group vs. placebo group (57% and 11%, respectively, p<0.05; S) but at week 8 it did not reach statistical significance; NS Remission rate at week 8 was higher in the celecoxib group vs. placebo group (57% and 11%, respectivel, p<0.05); S
Zdanowicz (2017)	Placebo	2 years	40 (ND)	ND	ND	ND	ASA (100 mg) + citalopram or ASA (100 mg) + duloxetine or placebo + citalopram or placebo + duloxetine	ND	"Regular" assessments with HAM-D and CGI scales	ND	BDNF serum levels measured 4 times yearly	ASA + duloxetine showed a quicker improvement in HAM-D and CGI scores vs. placebo + escitalopram (t=-3.114 p=0.01 and t=-2.119 p=0.05, respectively); S and NS, respectively ASA + duloxetine showed a higher remission rate vs. placebo + escitalopram ($\chi 2$=6.296 p=0.012); S ASA + duloxetine had higher BDNF levels before treatment vs. placebo + escitalopram (t=3.713 p=0.002); S

Legend: DSM-IV: Diagnostic and Statistical Manual for Mental Disorders, 4th edition; HAM-D: Hamilton depression scale (versions with different number of items); S: statistically significant; NS: not statistically significant; DSM-IV-TR: DSM-IV Text Revision; MIF: macrophage migration inhibitory factor; sCD14: soluble CD14; TGF-β: transforming growth factor-β; ELISA: enzyme-linked immunosorbent assay; ADAPT: Alzheimer's Disease Anti-inflammatory Prevention Trial; ND: not described; CAB: cognitive assessment battery; GDS-30: 30-item geriatric depression scale; 3MS-E: modified mini-mental state examination; IL-6: interleukin 6; ES: effect size; SCID: structured clinical interview for DSM-IV; HAM-A: Hamilton anxiety rating scale; ASA: acetylsalicylic acid; CGI: clinical global impression; BDNF: brain-derived neurotrophic factor.

TABLE 2: Study characteristics of identified non-RCTs.

Study					Population Characteristics		Treatment	Depression Assessment			Results
Source	Design (non-RCT)	Duration	Sample Size		% Male (Treatment / Control)	Age (years) (Treatment / Control)		Diagnostic Criteria	Outcome measure	Response Criteria	
			Enrolled (Treatment)	Analyzed (Treatment)							
Almeida (2010)	Retrospective	5 years	5 556 (ND)	5 273 (2 747)	100	Range 69-87 (ND)	Antidepressant treatment not reported. ASA self-reported use (610 past users of which 55 were depressed; 827 first time users of which 46 were depressed; 1 310 past and current users of which 78 were depressed)	GDS-15; presential MMSE	GDS-15 and presential MMSE, each assessed 2x	Same as outcome measure	Men with past and not current use of ASA had greater odds of displaying symptoms of depression vs. never users (AOR 51.41 95%CI 1.00-1.99 p=0.047); S Between the first and the second assessment, men with past and not current use of ASA had more contacts with health services vs. never users (p<0.001) and vs. first time users (p=0.01); S
Warner-Schmidt (2011)	STAR*D level-1 retrospective dataset reanalysis	12 weeks	ND	1546 (409)	ND	ND	NSAID + citalopram or NSAID + other analgesics + citalopram or other analgesics + citalopram or citalopram NSAIDs exposure defined by ≥ 1 consumption during study	ND	Remission at endpoint	Same as outcome measure	NSAIDs users were less likely to reach remission vs. NSAIDs non-users (p=0.0002); S Other analgesics users were less likely to reach remission vs. other analgesics non-users (p=0.0002); S NSAIDs plus other analgesics users were less likely to reach remission vs. NSAIDs or other analgesics non-users (p=0.0138); S NSAIDs or other analgesics users were less likely to reach remission vs. NSAIDs or other analgesics non-users (p<0.0001); S
Gallagher (2012)	A. i2b2 TRD Cohort – retrospective analysis of electronic medical record-based dataset	Variable [antidepressant treatment period, i.e. interval considered by a longitudinal classifier]	ND	1 528 (1 245)	29 (27 / 38)	Mean 51.9 (mean 53.0 ± 15.3 / mean 46.9 ± 17.6)	Maintained antidepressant treatment scheme (one or more). NSAIDs exposure defined by ≥ 1 documented prescription during the study (from medical record system); chronic treatment defined by ≥ 3 prescriptions (excluding as-needed basis only)	ICD-9 (Single Episode 296.2 or Recurrent 296.3)	"Validated longitudinal classifier"	Remission with SSRI monotherapy defined response; depression despite two or more antidepressant treatments defined resistance	NSAIDs associated with greater likelihood of treatment-resistant MDD (AOR 1.17 95%CI 0.83-1.64); NS NSAIDs other than COX-2 inhibitors and salicylates associated with greater likelihood of treatment-resistant MDD (AOR 1.31 95%CI 1.03-1.76 p=0.04); S Chronic NSAIDs users had higher risk of treatment-resistant MDD vs. NSAIDs non-users (AOR 1.47 95%CI 1.03-1.76 p=0.02); S
	B. STAR*D level-1 dataset reanalysis	12 weeks	ND	3 041 (960)	37.7 (40 / 37)	ND (mean 46.49 ± 13.29 / mean 39.23 ± 12.79)	NSAID + citalopram or citalopram NSAIDs exposure defined by ≥ 1 consumption during study; chronic / subacute treatment defined by NSAIDs use initiation ≥ 14 days before entering STAR*D	ND	QIDS at every visit (primary analysis); HAM-D at level entry and exit	Same as outcome measure	Applying CIRS-14 terms, adjusted logistic regression models markedly diminished the effect size; NS Chronic/subacute treatment group had higher odds of non-remission vs. NSAIDs non-users (AOR 1.44 95%CI 1.10-1.90 p<0.01); S
Uher (2012)	Partially randomized, clinical and pharmacogenetic study	12 weeks	811 (78 NSAIDs users, 43 of which took NSAIDs in a significant dose)	811 (78 NSAIDs users, 43 of which took NSAIDs in a significant dose)	36.6 (escitalopram group: 33 / 39; nortriptyline group: 50 / 33)	Mean 44.2 (escitalopram group: mean 47.1 ± 11.5 / 42.1 ± 11.7) (nortriptyline group: mean 45.7 ± 11.6 / 42.0 ± 11.9)	NSAIDs + citalopram (10-30 mg id) or citalopram (10-30 mg id) or NSAIDs + nortriptyline (50-200 mg id) or nortriptyline (50-200 mg id) NSAIDs use was ascertained weekly using a purpose-tailored medication form	DSM-IV / ICD-10 (semi-structured SCAN interview) – current depressive episode of at least moderate severity	MADRS, HAM-D-17 and BDI	MADRS ≤ 10, HAM-D-17 ≤ 7, BDI ≤ 10 at the last treatment visit defined remission	No effect on escitalopram (beta 0.035 95%CI -0.145-0.215) or nortriptyline (beta 0.075 95%CI -0.131-0.281) efficacy; NS Remission OR 1.04 95%CI 0.61-1.77; NS Older subjects were more likely to take NSAIDs; S

(continued)

TABLE 2: Study characteristics of identified non-RCTs (continued).

Glaus (2015)	CoLaus/PsyCoLaus Cohort – prospective study	Mean 5.2 years (± 1.2 years)	5 535 (ND). Exclusion criterion: lifetime history of MDD	1631 (87 regular ASA users; 92 regular statin users; 45 regular ASA and statin users)	56.4 (regular ASA users: 53.8 / 56.6; regular statin users: 64.2 / 55.7)	Range 35-66, mean 51.7 ± 8.8 (ND)	regular ASA users (132 subjects – 50% maintained during study) or regular statin users (137 subjects – 85% maintained during study) or ASA and statin non-users. Self-reported regular ASA and/or statin consumption concerned the 6 months prior to baseline	DSM-IV; semi-structured DIGS – diagnostic information on MDD, comorbid anxiety and drug use disorders; CES-D was applied to the 162 individuals not willing to complete DIGS	Incidence of first episode of MDD during follow-up – corresponding to 2,9% (± 211) of total individuals	Same as outcome measure	Regular ASA or statin use at baseline did not reduce the incidence of MDD during follow-up, regardless of sex or age (ASA: HR 1.19 95%CI 0.68-2.08; statin: HR 1.25 95%CI 0.73-2.14); NS
Kohler (2015)	Prospective population-based study - 25% representative random sample of Danish population (Danish Civil Registration System)	Total follow-up time: 53 697.8 person-years. SSRI incident initiators identified over a period of 10 years	1.375 million (ND). Exclusion criterion: antidepressant medication use in the preceding year	123 351 SSRI incident initiators (NSAID users: 17.5% (± 21 666), paracetamol users: 8.3% (± 10 232))	38.7 (NSAID + SSRI: 39.9: paracetamol + SSRI: 34.5; SSRI: 39.0)	Mean 50.9 IQR 35.4-70.6 (NSAID + SSRI 62.0 (45.3-76.8); paracetamol + SSRI 76.0 (62.9-83.8) / SSRI 46.5 (32.9-64.2)). ± 50% of combination therapy users had ≥ 70 years	NSAID + SSRI or paracetamol + SSRI or SSRI. NSAIDs prescriptions concerned the year prior to index date (Danish National Prescription Registry). NSAIDs: 4.9% used low-dose ASA, 2.6% used ASA, 5.1% used ibuprofen, 2.4% used diclofenac, 0.5% used celecoxib. SSRIs: 58.2% used citalopram, 16.2% used sertraline	ICD-10 Classification of Mental and Behavioural Disorders (DCR-10)	Hospital contact due to any psychiatric disorder or depression; completed suicide; suicide attempts	Same as outcome measure	NSAID + SSRI increased risks of any psychiatric contact (AHRR 1.22 95%CI 1.07-1.38) and contact with depression (AHRR 1.31 95%CI 1.11-1.55) vs. SSRI; S Low-dose ASA + SSRI and Ibuprofen + SSRI combinations decreased risk of psychiatric contact (AHRR 0.74 95%CI 0.56-0.98 and AHRR 0.76 95%CI 0.60-0.98, respectively) vs. SSRI; S Diclofenac + SSRI increased risks of any psychiatric contact (AHRR 2.60 95%CI 2.07-3.27), contact with depression (AHRR 4.47 95%CI 3.58-5.59) and suicide attempts (AHRR 3.20 95%CI 1.18-8.72) vs. SSRI; S Celecoxib + SSRI increased risks of contact with depression (AHRR 3.84 95%CI 2.40-6.13) and of suicide attempts (AHRR 5.09 95%CI 1.65-15.72) vs. SSRI; S Paracetamol + SSRI decreased risks of any psychiatric contact (AHRR 0.56 95%CI 0.44-0.71), contact with depression (AHRR 0.52 95%CI 0.37-0.74) and suicide attempts (AHRR 0.43 95%CI 0.20-0.92) vs. SSRI; S
Molero (2019)	SUN Cohort – prospective dynamic study	Mean 8.7 years	22 564 (ND). Exclusion criteria: lifetime history of MDD and antidepressant medication use	13 961 (453 regular ASA users, 216 regular other NSAIDs users)	ND. Participants' baseline characteristicswere adjusted for sex with inverse probability weighting method	ND. Participants' baseline characteristics were adjusted for age with inverse probability weighting method	ASA and other NSAIDs intake was assessed at 2-, 6-, 8- and 14-year follow-up questionnaire. Daily use or more (≥ 1 time per day) defined regular use of the drug, comparatively to the reference category of no consumption at all	Reported medical diagnosis of MDD or reported use of antidepressant treatment defined incident cases of MDD (mailed questionnaire every 2 year)	Incidence of first episode of MDD during follow-up – corresponding to 5,5% (± 772) of total individuals. Validated medical diagnosis of MDD was studied in a sub-sample of the cohort	Same as outcome measure	Regular use of ASA and other NSAIDs was not associated with depression risk vs. NSAIDs non-users (MHR (ASA) 0.84 95%CI 0.41-1.722 and MHR (other NSAIDs) 1.33 95%CI 0.59-2.99); NS Any frequency of use of NSAIDs (other than ASA) showed higher risk of developing depression among participants vs. NSAIDs non-users (MHR 1.90 95%CI 1.15-3.17); NS after adjustment for multiple testing Validated medical diagnosis of depression altered the association for ASA use and depression (MHR 0.20 95%CI 0.04-0.87); NS after adjustment for multiple testing

Legend: ND: not described; ASA: acetylsalicylic acid; GDS-15: 15-item geriatric depression scale; MMSE = mini-mental state examination; AOR: adjusted odds ratio; S: statistically significant; STAR*D: Sequenced Treatment Alternatives to Relieve Depression; NSAID(s): nonsteroidal anti-inflammatory drug(s); TRD: treatment-resistant depression; ICD: International Classification of Diseases (various revisions); SSRI: selective serotonin reuptake inhibitor; MDD: Major depressive disorder; NS: not statistically significant; COX-2: cyclooxygenase-2; QIDS: quick inventory of depressive symptomatology; HAM-D: Hamilton depression scale (versions with different number of items); CIRS-14: 14-item cumulative illness rating scale; DSM-IV: Diagnostic and Statistical Manual for Mental Disorders, 4th edition; SCAN: schedule for clinical assessment in neuropsychiatry; MADRS: Montgomery–Asberg depression rating scale; BDI = Beck depression inventory; OR: odds ratio; DIGS = diagnostic interview for genetic studies; CES-D: Center for Epidemiologic Studies depression scale; HR: hazard ratio; IQR: inter quartile range; DCR-10: diagnostic criteria for research related to ICD-10; AHRR: adjusted hazard rate ratio; SUN: Seguimiento Universidad de Navarra; MHR: multivariable-adjusted hazard ratio.

3.2.2 Non-RCTs

A dichotomized analysis was required for the eight non-RCT studies, owing to distinct differences in the mental health state of the cohorts: those studying a depressed population and those studying non-depressed participants.

3.2.2.1 Non-RCTs in depressed subjects

Five studies targeted a depressed population to explore the effect of NSAIDs on depressive symptoms (n=130 277). Two of these - one retrospective and the other prospective - revealed an overall significant negative effect of NSAIDs on depressive symptoms (n=124 897). The remaining three studies demonstrated no significant effect (n = 5380).

In the study by Gallagher *et al*. (2012), with the overall conclusion of a significant negative effect, the authors ran a secondary analysis distinguishing between the different NSAIDs, and concluded that only NSAIDs other than COX-2 inhibitors and salicylates significantly associated with a greater likelihood of treatment-resistant MDD [25]. Kohler *et al*. (2015) also analysed different NSAID categories and found that ibuprofen and salicylates (in particular low-dose ASA) yielded a lower risk of any hospital contact due to psychiatric disorders, whereas diclofenac and selective COX-2 inhibitors (in particular celecoxib) increased this risk – the former also increased hospital contacts due to depression while and the latter was associated with a higher risk of suicide attempt [26].

Inflammation was not assessed in any of these five studies. Heterogeneity was noted regarding exposure and outcome assessment; NSAIDs exposure contemplated either prescription records, dispensed prescription drug records or reported use only. Treatment chronicity definition also varied, being measured either by number of prescriptions or by duration of treatment. For outcome evaluation, all authors applied different measuring tools. The study by Kohler *et al.* (2015) investigated a population of SSRI incidental users, without considering indication [26]. The most frequently studied antidepressant agent was citalopram, while NSAID subgroups were considered separately in only two studies.

There was minor variability amongst the four studies that described participants' age ranges, and means were mostly under 65 years of age. Three studies adjusted for age and comorbidities, one of which also adjusted for baseline severity and pain. The partially randomized clinical trial adjusted for age and baseline severity. One study did not describe participants' age range or present adjusted results.

3.2.2.2 Non-RCTs in non-depressed subjects

The three remaining non-RCTs, one retrospective and two prospective studies, were conducted on non-depressed participants, exploring the effect of NSAIDs as a protective measure (n=20 865). All three concluded that there was no significant effect of NSAIDs on MDD incidence.

Inflammatory status was only assessed in the study by Glaus *et al*. (2015), where homocysteine serum concentration above 15 µmol/L was defined as a biological risk factor [27]. However, the small size of the at-risk subgroup did not allow for any conclusions to be drawn.

The three studies resorted to self-reported treatment with ASA, two of which evaluated no other NSAIDs use. All had a considerably long follow-up (at least 5 years).

Heterogeneity was noted in terms of outcome measures, with all studies applying different assessment tools. Two studies evaluated "regular" NSAIDs use, although applying different definitions thereof. Again, one of the studies did not describe participants' ages, but in the remainder there was minor variability (mostly over 65 years of age).

Results presented in these three studies were adjusted for age and smoking status. Additionally, one study adjusted for various biological risk factors such as homocysteine [27], another for multiple hypothesis testing [28] and a third adjusted for cardiovascular diseases, arthritis and other comorbidities [29].

4. Discussion and Conclusion

This comprehensive review aimed to provide an updated overview of studies that investigate NSAIDs as a therapeutic tool for MDD. Inclusion criteria were set to evaluate its use as monotherapy or as adjunct to treatment with antidepressant drugs, irrespective of cohort demographics. Following the systematic retrieval procedure, a total of 14 records were selected, pertaining to 15 clinical trials.

A general analysis of the 15 studies suggested that NSAIDs may have a positive effect in the treatment of MDD, in particular when administered as adjunct to antidepressants. However, given the methodological heterogeneity amongst the studies, a breakdown into subgroups was required for critical assessment with adequately weighted conclusions. From the outset, they were divided into RCTs and non-RCTs.

A total of seven RCTs were analysed, six of which demonstrated a significant positive effect of NSAIDs as adjunctive treatment (n=230). The seventh RCT investigated NSAIDs as monotherapy (n=2 528), concluding that there was no significant effect. This RCT comprised the oldest age group (70-91yr), was not uniform in terms of depression classification and biological markers for inflammation were not measured. The three RCTs that considered immune parameters (at baseline and at least at trial-end) all assessed different markers. In one of these studies, that measured MIF, sCD14 and TGF-β, no significant differences were found, whereas in the other two RCTs, that individually assessed IL-6 and BDNF serum levels, these markers were seen to exhibit a significant correlation with HAM-D scores. As a whole, between the seven RCTs heterogeneity was most evident with respect to the therapeutic scheme and the outcome definition.

Our findings are largely in agreement with those recently documented by Bai *et al*. (2020) in a meta-analysis that aimed to assess efficacy as well as safety of several anti-inflammatory agents [30]. In a subgroup meta-analysis they examined four RCTs (n=152) in common with our selection (namely those of Müller 2006, Akhondzadeh 2009, Abbasi 2012 and Majd 2015) and concluded that celecoxib combined with antidepressants were better than antidepressants alone, leading to a significantly larger reduction in HAM-D-17 scores. Other anti-inflammatory agents such as omega-3, fatty acids, statins and minocycline also showed a significant antidepressant effect when used as adjunctive treatment to SSRI or SNRI (Selective Noradrenergic Reuptake Inhibitors), and the same agents were also found to be effective as monotherapy, although with a smaller effect size. Their analysis did not include RCTs with NSAID monotherapy.

Earlier reviews have also included different subsets of our selected RCT studies. Köhler *et al*. (2014) analysed ten clinical trials (n=4258) studying NSAIDs in the treatment of MDD as well as a wide range of depressive symptoms [31]. Overall, NSAID treatment was found to be associated with a positive antidepressant effect. A subgroup analysis of celecoxib (n=2750) revealed a more relevant beneficial effect, particularly as adjunctive treatment. This celecoxib subgroup included four RCTs in common with our analysis; three evaluating NSAIDs as adjunctive treatment (Müller 2006, Akhondzadeh 2009 and Abbasi 2012) and one as monotherapy (Fields 2012). The same three RCTs with NSAID adjunct therapy were also assessed in two other meta-analyses [32] [33], both reporting a medium to large effect size for regimens that combine celecoxib with antidepressants. Firstly, the subgroup analysis by Faridhosseini *et al*. (2014), which included four RCTs (n=160), revealed a significant decrease in the means of HAM-D-17 scores and significant treatment and remission responses [32]. Similarly, the subgroup analysis by Na *et al*. (2014), comprising four RCTs (n=150), concluded that patients receiving adjunctive celecoxib had significantly higher mean changes in the HAM-D-17 scores between baseline and endpoint measurements compared with those receiving placebo, as well as improvement in terms of remission and response rates [33].

In a systematic review, Allison *et al*. (2019) sought to analyse the efficacy of several anti-inflammatory treatment strategies as determined by changes in concentrations of inflammatory mediators, focussing on MDD patients that demonstrated elevated baseline inflammation [34]. This narrative analysis identified a single RCT (n=40) that showed a significant decrease of the elevated baseline inflammation marker C-reactive protein (CRP), following a non-drug intervention (meditative walking). Even so, the endpoint CRP concentrations did not reach the normative values and this RCT presented a high risk of bias. Amongst the five RCTs that tested pharmaceuticals, only one (Abbasi 2012), with a celecoxib regimen (n=37), demonstrated a significant decrease of the baseline inflammatory marker IL-6. Notwithstanding, baseline IL-6 concentrations fell within the normative value range for this parameter, and the placebo group also had a significant, albeit lower, IL-6 concentration decrease [34]. Besides this RCT, our review identified a study with a longer duration period, where BDNF measurements had been made at baseline and four times yearly (Zdanowicz 2017). This RCT tested ASA versus placebo, combined with either citalopram or duloxetine (n=40). The best response, as per Ham-D/CGI scores as well as per remission rates, was observed in the scheme using ASA plus duloxetine. As compared to the rest, this subgroup of patients revealed a statistically significant difference in terms of higher BDNF levels before treatment, leading the authors to conclude that either a noradrenergic agent combined with

ASA is more effective than a serotonergic agent alone, or the level of baseline BDNF is a precursor marker of the response to antidepressants. Further evidence favouring a differential response according to baseline inflammation had been provided in an earlier study by Raison *et al*. (2013); here the sample size (n=22) posed a limitation to statistical significance, but results pointed towards a clinically meaningful effect of anti-inflammatory agents in patients with higher baseline CRP levels [35].

Of the eight non-RCTs included in our analysis, five targeted a depressed population (n=130 277), with evident heterogeneity regarding exposure and outcome measures, and with no inflammation assessment. Three of these studies (Gallagher 2012 studies A and B, and Uher 2012) found no significant effect of NSAIDs on depressive symptoms (n=5 380), with results being adjusted for age, Charlson Comorbidity Index and/or baseline severity. The remaining two studies (Warner-Schmidt 2011 and Kohler 2015) concluded that NSAIDs had an overall significantly negative effect on depressive symptoms (n=124 897).

Subgroup analyses of adverse effects demonstrated that different NSAID categories presented different risk profiles. In particular, selective COX-2 inhibitors and salicylates were positively highlighted by Gallagher *et al.* (2012), while Kohler *et al.* (2015) identified favourable results for ibuprofen and low-dose ASA [25] [26]. The latter study, however, investigated a population of SSRI incidental users, without considering indication. In this case, caution should be taken when extrapolating the results to MDD patients, as SSRI may be used to treat other disorders, such as anxiety [26].

The remaining three non-RCTs (n=20 865) chose to study non-depressed subjects in order to evaluate the effect of NSAIDs as a protective measure, all concluding that there was no significant effect of NSAIDs on MDD incidence, with results adjusted for age and smoking status. Here again, this group presented heterogeneity in terms of outcome measures and no conclusive results as to subjects' inflammatory profiles.

Considering the complex and chronical evolution of MDD, the study designs of the analysed RCTs and non-RCTs as a whole, are far from ideal. With such small sample sizes and short follow-up durations, particularly in the RCTs, quality of life measurements would hardly show any significant improvement. Additionally, these limitations impair the evaluation of long-term efficacy and the assessment of late-onset adverse events [30].

The lack of systematic inflammation assessment, measuring the levels of specific and impactful pro-inflammatory mediators, hinders an extensive analysis of the data. Standardized reference values are also yet to be established for most of these markers [34]. Moreover, although it is

accepted that pro-inflammatory factors play a role in the pathophysiological mechanisms underlying MDD (as schematized in part in Figure 1), the baseline and profile of their levels over time need to be taken into consideration, as there is growing evidence of their beneficial or even critical roles when present in "healthy" concentrations, namely in neurogenesis, neural plasticity and synaptic strengthening [34].

In recent years, more specific inflammatory mechanisms have also been targeted. Several monoclonal antibody therapies have been studied, aiming to reduce depressive symptoms through TNF-α antagonism. Significant antidepressant effects were demonstrated for etanercept (a TNF-α receptor and IgG1 Fc fusion protein), adalimumab (a human monoclonal anti-TNF-α antibody) and ustekinumab (a human monoclonal anti-IL-12 and IL-23 antibody) [7]. However, the samples in these three studies all comprised patients with moderate to severe psoriasis, and the authors had to admit that the observed parallel amelioration in psoriatic symptoms was a possible source of confounding to the antidepressant effect [7]. Infliximab (a chimeric monoclonal anti-TNF-α antibody) has also been extensively studied, but its effect as antidepressant was not demonstrated to be significant in cohorts either with treatment resistant MDD or with high baseline pro-inflammatory levels [7]. IL-6 has progressively become a target too. Recently, siltuximab (a chimeric monoclonal anti-IL-6 antibody) was shown to significantly reduce the prevalence of depressed mood and anhedonia, compared to placebo, in a population of Multicentric Castleman's Disease patients, even after disease severity adjustments [7].

In fact, in order to address MDD as a pro-inflammatory entity on its own, our study avoided such sources of confounding by excluding all studies using patients with major co-morbid inflammatory conditions. For instance, pain is frequently a confounding factor, since MDD-related improvements can be indirectly attained by pain relief itself.

Besides avoiding co-morbidities, future studies need to address the heterogeneity that characterizes MDD's pathophysiology and presentation; one such example is that only a subset of patients seem to have a pathologically augmented inflammatory state underlying their psychiatric disease. Yehia *et al.* (2019) question the power of large numbers whenever searching for meaningful clinical data, suggesting the more "elegant" and "pragmatic" approach of deep phenotyping [36]. Selective patient recruitment based on specific disease manifestations creates a level of uniformity that simplifies the identification of disease modifiers and enables new insights into the underlying pathophysiological pathways [36]. Indeed, by integrating phenotypical with multi-omics data, Kluiver *et al.* (2019) concluded that

MDD patients with hyperphagia – defined as increased appetite and/or weight – had significantly higher inflammatory pathway-related expression profiles [37]. Relevant pathways identified were those of several transcription factors and of caspases. Their findings led them to propose, for instance, that the augmented caspase-1-related pathways may be associated with MDD through their contribution to the glucocorticoid resistance process and, thereby, to the HPA axis hyper-activation [37].

In this era of the "omics", it should be feasible to carry out RNA and/or protein expression studies in other phenotypically well-defined subgroups of MDD patients, or even incorporate genotypic data generated from genome-wide association studies. In the quest for personalized medicine, pharmacogenomics may assume a first-tier test to identify the ideal treatment strategies at least for certain subgroups of MDD patients.

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Competing Interests:

The authors declare no conflicts of interest.

ANEXOS

ANNEXES

ANEXO 1 */ ANNEX 1*

Progress in Neuro-Psychopharmacology & Biological Psychiatry

Author Guidelines

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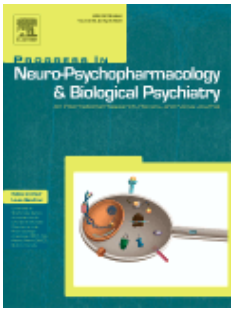

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ANEXO 2 */ ANNEX 2*

Progress in Neuro-Psychopharmacology & Biological Psychiatry

Highlights for publication

Highlights

- Several pro-inflammatory pathways seem to underlie Major Depression Disorder.
- Nonsteroidal anti-inflammatory drugs may be beneficial as add-on therapy.
- Heterogeneity between studies still hinders solid evidence-based conclusions.
- Deep phenotyping in future studies may uncover the role of anti-inflammatory drugs.

ANEXO 3 */ ANNEX 3*

Abstract submitted for presentation at the

33rd Annual Congress of the European College of Neuropsychopharmacology

Vienna, 12-15th September 2020

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Beatriz Caldeira <beascaldeira@gmail.com>

abstract ECNP

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Abstract title NSAIDS IN THE TREATMENT OF MAJOR DEPRESSIVE DISORDER – FROM THE FLORET TO THE THREE, A COMPREHENSIVE REVIEW

Co-authors

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TopicsMood disorders
Pharmacological interventions

Background/Objectives: The inflammatory hypothesis in the aetiology of depression raised the opportunity for new therapeutic tools as first line, adjunctive or symptomatic treatment of Major Depressive Disorder (MDD) [1,2]. However, studies assessing the efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) and systematic reviews and meta-analyses of these studies carried out over the last few years have yielded contradictory results [3,4]. The present review provides an updated overview of such studies with the aim of clarifying the effectiveness of NSAIDs as therapeutic strategies in patients with MDD.

Methods: A literature search was conducted in accordance with the PRISMA guidelines. Searches were conducted in the English language, from inception to the 14th January 2020, to retrieve clinical trials using nonsteroidal anti-inflammatory drugs (NSAIDs) for the treatment of MDD.
Besides the completed randomised and controlled clinical trials (RCTs), non-randomised and non-placebo-controlled trials were also included in the search. Studies with NSAIDs as monotherapy and/or as adjunct of antidepressant therapies across all age groups were included to tentatively strengthen the qualitative assessment of NSAID effectiveness. Relevant articles, published prior to January 2020 were retrieved by querying eight databases, namely PubMed, Google Scholar, PubMed Central, Web of Science, JAMA Psychiatry, ClinicalTrials.gov, Cochrane Central Register of Controlled Trials and ICTRP. Additional articles were manually scrutinized from bibliography listings of the selected articles.

Results: Fourteen records, comprising 15 clinical studies, were identified for inclusion in the qualitative synthesis. Seven RCTs investigated the efficacy of NSAIDs in a total of 2 758 patients. Six of these demonstrated a significantly positive effect when used as adjunctive treatment, and one demonstrated no effect as monotherapy.
Among the remaining 8 studies, non-RCTs, five analysed the effect of adjunctive NSAIDs treatment on the depressive symptoms of 130 277 patients from which four revealed a significantly negative effect and one showed no effect. The other three non-RCTs, conducted on a total of
20 865 non-depressed participants, failed to confirm the preventive effect of NSAIDs. Internal and external validity is compromised by study designs. In particular, most RCTs had small sample sizes and short follow-up durations. Additionally, heterogeneity was noted in terms of outcome and exposure assessments, therapeutic schemes as to drug combinations and dosage, as well as covariates applied for result adjustments.

Conclusions: Overall, NSAIDs may exert a beneficial therapeutic effect in MDD as an adjunctive treatment to antidepressants, although methodological heterogeneity introduces some inconsistencies. NSAIDs appear to have no effect as a preventive measure in MDD, particularly amongst the elderly. Study designs need to address the highly heterogeneous pathophysiology and presentation of MDD by deep phenotyping, and by targeting specific inflammatory mechanisms. Patient selection, uniformity, together with well-matched controls, can provide statistically powerful and clinically meaningful data. Genotypic profiling would ultimately contribute towards a better understanding of the role inflammation, and anti-inflammatory drugs, in MDD.References

□1□ Miller, H.A., Raison, C.L. (2016). The role of inflammation in
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(2019). Efficacy and safety of anti-inflammatory agents for the treatment of major depressive disorder: a systematic review and meta-analysis of randomised controlled trials. J Neurol Neurosurg Psychiatry. jnnp-2019-320912 DOI: 10.1136/jnnp-2019-320912 □4□ Kohler, O., Krogh, J., Mors, O., Benros, M.E. (2016).
Inflammation in Depression and the Potential for Anti-Inflammatory Treatment. Curr Neuropharmacol.14(7),732–742.

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