SYSTEMATIC REVIEW ARTICLE

Exploring the Influence of Inflammation on the Pharmacokinetics of Antidepressants and Antipsychotics: A Systematic Review

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Abstract: ***Introduction/Objective*:** Strong evidence suggests that inflammation can affect the activity of Cytochrome P450 (CYP) isoforms responsible for the metabolism of numerous psychiatric drugs. This is likely of particular importance in conditions such as Major Depressive Disorder (MDD), where a relevant percentage of patients report non-response to treatment. Thus, the existing knowledge on the impact of inflammation on medications used in MDD, and metabolised *via* these pathways (*e.g.*, antidepressants and antipsychotics), needs to be further evaluated.

***Methods*:** In this systematic review, the PubMed, Scopus, and Web of Science databases were screened, and published articles between January 1st, 2010, and May 25th, 2025, were retrieved. The research strategy was based on combinations of key terms related to pharmacokinetics, inflammation, and antidepressants or antipsychotics. A total of five observational and cohort studies were included, along with ten case series or case reports that investigated the topic in human subjects.

***Results/Discussion*:** The available evidence appears unbalanced and severely limited for antidepressants. The single study available suggests limited changes in the pharmacokinetics of citalopram and venlafaxine in inflammatory conditions. By contrast, the available data for antipsychotics suggest variable effects of inflammation on their pharmacokinetics. In particular, clozapine is associated with substantial increases in plasma concentrations. Overall, the relationship between inflammation and the pharmacokinetics of psychiatric drugs appears to be complex. Furthermore, much of the available data is plagued by limitations, such as small sample sizes and retrospective designs, as well as poor characterisation of patients' genetic and immunological profiles.

***Conclusion*:** Considering the current, very limited evidence base, especially for antidepressants, the necessity for larger prospective studies remains pressing. Further studies should incorporate pharmacogenetics and immunological profiling to better support clinical practice recommendations.

Keywords: Antidepressants, antipsychotics, pharmacokinetics, inflammation, therapeutic drug monitoring, drug plasma levels.

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1. INTRODUCTION

Inflammation is a highly conserved physiological response that aims to eliminate harmful stimuli, promote tissue repair, and restore homeostasis [1]. It involves a complex cascade of immune signalling pathways and cellular actors, both in the periphery and within the Central Nervous System (CNS) [2]. Chronic, low-grade inflammation can become maladaptive and has been increasingly recognised as a common feature in a wide array of non-communicable diseases, including cardiovascular pathologies, diabetes, cancer, and neurodegeneration-related diseases [3, 4]. Furthermore, persistent inflammation is capable of altering neuroendocrine, metabolic, and behavioural processes [5]. Converging evidence has underscored the pivotal role of inflammation in shaping brain function, highlighting its importance in psychiatric conditions [6]. For instance, Major Depressive Disorder (MDD) is characterised by considerable clinical and biological heterogeneity, making its treatment challenging [7]. Apart from the current monoaminergic dysregulation hypothesis of MDD [8-10], emerging data suggest that immunological processes may be involved in some patient subgroups [11, 12]. Specifically, a growing body of evidence shows that some individuals with MDD may exhibit elevated peripheral levels of pro-inflammatory cytokines such as Interleukin (IL)-6, Tumour Necrosis Factor-alpha (TNF-α), and IL-1β [7, 13-15]. Consequently, some of these patients may not respond adequately to conventional antidepressant therapies [9].

The presence of systemic low-grade inflammation could substantially increase the variability in drug exposure and, therefore, response to pharmacological treatments [16-18]. The hepatic cytochrome P450 (CYP) isoenzymes, particularly CYP2C19, CYP2D6, and CYP3A4, can be downregulated by pro-inflammatory cytokines, such as IL-6 and TNF-α [19, 20]. These isoenzymes are fundamental for the metabolism of the majority of antidepressants, such as Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) [21]. However, antidepressants are not the only drug class used in the treatment of MDD. In patients who exhibit Treatment-Resistant forms of Depression (TRD), as well as MDD with psychotic features, antipsychotics are frequently used as add-on therapies [22, 23]. Antipsychotics are also metabolised by the same CYP isoforms just as antidepressants [24]. Thus, systemic inflammation conditions may alter the pharmacokinetics of pharmacological treatment for MDD [25].

Adding further complexity, growing evidence indicates that both antidepressants and antipsychotics can, in turn, modulate immune and inflammatory processes, although findings are not always consistent across experimental models [26, 27]. For antipsychotics, literature sources emphasise that alterations in inflammatory markers may vary highly depending on the specific drug, experimental model, and context, sometimes even demonstrating opposing outcomes for the same compound [28].

In light of these considerations, it becomes apparent that inflammation may represent a clinically relevant but still insufficiently characterised modulator of treatment exposure and, by consequence, response in patients treated with these drug classes. Therefore, this systematic review aims to provide a critical appraisal of the available literature on the influence of inflammatory processes on antidepressant- or antipsychotic-based treatments.

2. METHODS

2.1. Search Strategy

The identification, screening, and extraction of relevant data were performed in accordance with the PRISMA ("Preferred Reporting Items for Systematic Reviews and Meta-Analyses") 2020 guidelines [29]. A systematic search was independently conducted by two authors (GC, MAB) using the academic databases PubMed, Scopus, and Web of Science (WOS) databases. In addition, the academic search engine Google Scholar was consulted. All sources were last consulted on May 25th, 2025. For PubMed, the query combined MeSH (Medical Subject Headings) terms and free-text keywords related to inflammation, antidepressants or antipsychotics, pharmacokinetics, and/or blood concentrations. Filters were also applied to the query to exclude reviews and to include studies on humans, written in English, and published between January 1, 2010, and May 25, 2025. The 2010 threshold was set to balance search completeness with alignment to modern research standards. In Scopus, the search was conducted using text terms for inflammation and antidepressants or antipsychotics, in combination with pharmacokinetics-related terms, further restricted to human studies, and filtered by publication year. In WOS, a similar query structure was used, applying filters for document type (original articles), language (English), study population (humans), and publication years (2010-2025). Additionally, the reference lists of all included articles were manually screened to identify potentially relevant studies that may have been missed. The complete query formulations for each data source, including Boolean logic, truncations, and field-specific adaptations, are reported in Supplementary Box 1.

2.2. Inclusion and Exclusion Criteria

Data sources were considered eligible for inclusion if they met the following criteria: (i) original research articles or case reports; (ii) focused on the pharmacokinetics of one or more antidepressant or antipsychotic agents; and (iii) conducted in human subjects. Data sources were excluded if (i) they were non-original articles such as reviews and editorials; (ii) they were preclinical or animal studies; (iii) they did not report primary pharmacokinetics data; (iv) they did not report clear inflammatory status measures or proxies; and (v) they were not written in English. The adherence of the retrieved sources to the aforementioned criteria was evaluated independently by two authors (GC and MAB). Record management and duplicate removal were handled using Microsoft Access©.

2.3. Risk of Bias Evaluation and Critical Appraisal

The risk of bias was evaluated in observational studies using the modified Newcastle-Ottawa Scale [30, 31] to assess the quality of non-randomised studies. For case reports and series, the Joanna Briggs Institute critical appraisal tools were used [32, 33]. Both evaluations were conducted

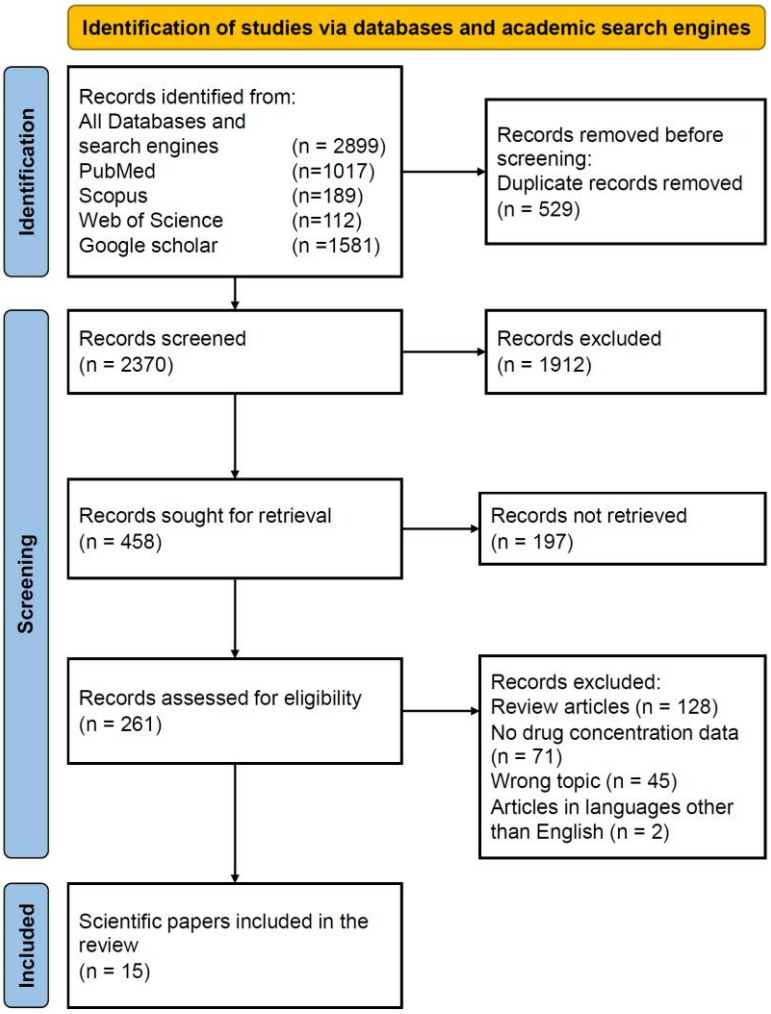

Fig. (1). PRISMA compliant record extraction and processing flow diagram. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

independently by two authors (GC and AG in one case, and MAB and NC in the other). Evaluation conflicts were resolved by a third author (ES in the first case and AC in the second).

3. RESULTS

3.1. Included Data Sources Characteristics

After the database scraping and record processing, a total of 261 literature sources were assessed for eligibility. Among those, 15 were found to be compliant with the selection criteria and further analysed (see Fig. **1** for details). The retrieved data can be divided into two levels of evidence. First, a limited number of observational studies have addressed this topic, either for antidepressants or antipsychotics. Specifically, four studies were identified for antipsychotics, and one for antidepressants. A synthesis of the characteristics of these studies is provided in Table **1**. Most of these studies exhibited a moderate to high risk of bias. This was primarily due to limited control for key confounders, including smoking status, concomitant medications, and infection severity. Further details can be found in Supplementary Table **1**. Second, several case reports and case series, focused on antipsychotics, provided clinical evidence of acute, inflammation-driven pharmacokinetic alterations. For case reports and series, the available evidence includes eight sources for Clozapine (CZP) and two for Risperidone (RIS). A synthesis of the characteristics of these anecdotal sources is provided in Table **2**. The results of the critical appraisal for each anecdotal source are provided in supplementary Tables **2** and **3**. In addition, details on the estimated percentage variations in concentration-to-dose (C/D) ratios reported in observational studies are available in Supplementary Table **4**. At the same time, those related to anecdotal sources are available in Supplementary Table **5**.

3.2. Inflammation and Antidepressants Pharmacokinetics

3.2.1. Citalopram

Citalopram (CIT) is an SSRI widely prescribed for the treatment of major depressive disorder and other affective disorders [34]. CIT is a bicyclic phthalane derivative and exerts its main antidepressant effect by blocking serotonin (5-HT) reuptake in the central nervous system to increase the synaptic concentration of serotonin [35]. CIT is extensively metabolised in the liver, predominantly *via* cytochrome P450

Table 1. Systematic studies and observational cohorts on the impact of inflammation on antidepressant and antipsychotic pharmacokinetics.

Author (Year)	Study Type	Population	Diagnosis/Setting	Index Drug(s)	Dose/Range	Inflammatory Marker	Main PK Finding(s)	Clinical Outcome(s)
Hefner *et al*., 2015a	Retrospective intra-individual TDM	15 CIT, 39 VEN	Psychiatric in/outpatients	CIT, VEN	Steady-state	CRP <5 vs ≥5 mg/L	No significant change in C/D or MR for either drug	None
Hefner *et al*., 2015b	Retrospective intra-individual TDM multi-drug	33 CZP, 32 QUE, 40 RIS	Psychiatric in/outpatients	CZP, QUE, RIS	Steady-state	CRP <5 vs ≥5 mg/L	CZP: C/D +48% (p<0.01); QUE: C/D +11.9% (p=0.053); RIS+PAL: C/D+24.2% (p=0.003); all MR as above	None severe
Scherf-Clavel *et al*., 2019	Retrospective TDM, multi-drug	166 QUE, 45 RIS, 24 OLA, 30 ARI	Psychiatric in/outpatients	QUE, RIS, OLA, ARI	See text	CRP ≥ 5 mg/L	QUE: ↑C/D w/CRP; OLA: trend; RIS/ARI: ns	QUE 8% >500 ng/mL
Ruan *et al*., 2020	Retrospective	16 adults	Schizophrenia, hospital setting	CZP	200-300 mg/day	infection episodes, CRP/leukocytosis	Mean C/D ratio ~1.5-2.5 (no infection) vs. ~3-6 (infection);	61% required 50% dose reduction, 28% required 66% reduction
Smith *et al*., 2025	Retrospective cohort,	60 adults (30 smokers, 30 non-smokers)	Psychiatric inpatients	CZP	Variable (TDM-guided)	CRP <5, 5-50, >50 mg/L + smoking	Non-smokers: C/D ×3 in high CRP; smokers: ns	High-CRP non-smokers: risk

Abbreviations: AD = antidepressants; AP = antipsychotics; ARI = aripiprazole; C = plasma concentration; C/D = concentration-to-dose ratio; CIT = citalopram; CZP = clozapine; CRP = C-reactive protein; FEP = first-episode psychosis; MR = metabolic ratio; ns = not significant; OLA = olanzapine; PK = pharmacokinetics; QUE = quetiapine; RIS = risperidone; TDM = therapeutic drug monitoring; VEN = venlafaxine.

Table 2. Case reports and case series on inflammation-related pharmacokinetic changes in antipsychotic therapy.

Author (Year)	Study Type	Population	Diagnosis/Setting	Index Drug	Dose	Inflammatory Marker	Main PK Finding(s)	Clinical Outcome(s)
Espnes *et al*., 2012	Case report	1M, 23y	Schizophrenia, gastroenteritis	CZP	900 mg/d	CRP 130 mg/L	CZP 9,074 nmol/L, NCZP/CZP ratio drop	Mild symptoms; AGP ↑
Farha *et al*., 2012	Case report	1M, 44y	Schizophrenia	CZP	300 mg/d	CRP 130 mg/L	CZP 1,301 µg/L, NCZP/CZP ratio 0.4	Paralytic ileus; resolved after ABX/↓dose
Štuhec, 2013	Case report	1F, 80y	Dementia + psychosis	CZP	25 mg/d	CRP 122 mg/L	CZP ↑ with fever	Mild symptoms, recovery
Leung *et al*., 2014	Case series	3 adults (32-52y)	Schizophrenia/SzA, infection	CZP	250-800 mg/d	CRP 56-217 mg/L	CZP 1,400-4,318 ng/mL, ratio ↑	ICU admission, toxicity
Buist & Schauer, 2015	Case report	1F, 57y	Schizoaffective + fever	CZP	Up to 300 mg/d	CRP 211 mg/L	CZP ↑ to 3,280 nmol/L	Mild symptoms; rapid drop after ↓dose
Hefner *et al*., 2015	Case report	2F (38, 56y)	Psychosis, infection	RIS	6 mg/d	CRP 105/110 mg/L	The active moiety tripled	Mild rigidity in one
Helland *et al*., 2018	Case report	1M, (56y)	Schizophrenia, infection	RIS	8 mg/d	CRP 36→405 mg/L	Active moiety ×4.9	No toxicity, dose reduction
Ruan *et al*., 2018	Case report ×2	1F (57y), 1M (47y)	Schizoaffective disorder	CZP	200-375 mg/d	CRP ↑; dermatitis or influenza	C/D ↑ by 1.45 (F, dermatitis), ↑ by 2.56 (M, influenza); total C/D ↑ from 3.10→3.90 and 1.59→3.46	No toxicity symptoms despite levels >1000 ng/mL
Arrojo-Romero *et al*. 2022	Case series	2F (49, 61y) 3M (64, 69, 37y) 1 NA (54y)	Schizophrenia	CZP	200-400 mg/day	CRP (mild ↑ in 4, marked ↑ in 2 with pneumonia)	C/D ratio ~0.7-2.5 (no infection) vs. up to 3.3 (COVID-19 infection)	2/6 required dose reduction (50% and 33%) due to severe symptoms/CRP ↑; no deaths
Shelton *et al*., 2022	Case series	3 (19-23y)	FEP, titration	CZP	50-125 mg/d (see text)	CRP up to 37 mg/L	Case 1: 3 troughs >600 ng/mL on ≤150 mg/d Case 2: [CZP] 595 ng/mL on 200 mg/d Case 3: [CZP] 453 ng/mL on 200 mg/d; 423 ng/mL on 12.5 mg/d (rechallenge)	Toxicity, myocarditis, recovery

Abbreviations: AGP = alpha-1-acid glycoprotein; C = plasma concentration; C/D = concentration-to-dose ratio; CZP = clozapine; CRP = C-reactive protein; FEP = first-episode psychosis; ICU = intensive care unit; MR = metabolic ratio; PK = pharmacokinetics; RIS = risperidone; SzA = schizoaffective disorder; TDM = therapeutic drug monitoring; NA = not available.

isoenzymes CYP2C19, CYP3A4, and to a lesser extent CYP2D6. The main metabolites of citalopram are N-desmethylcitalopram (NDCIT) and didemethylcitalopram. These metabolites also exhibit a certain level of pharmacological activity. However, their effects are considerably diminished compared with those of their parent compound and do not appear to contribute significantly to the overall therapeutic effect [36]. The current evidence regarding the effect of inflammation on CIT pharmacokinetics is limited to a single study. Hefner *et al*. conducted an intra-individual Therapeutic Drug Monitoring (TDM) study. The CIT cohort comprised 15 psychiatric patients (9 women, 6 men; median age, 65 years; 60% aged 65 or older). For each subject, paired serum steady-state samples were collected. One with C-Reactive Protein (CRP) levels < 5 mg/L and the other with CRP levels ≥ 5 mg/L. The parameters examined were the dose-corrected CIT C/D, NDCIT C/D, and the NDCIT/CIT metabolic ratio. The median C/D for CIT was 2.85 ng/mL/mg (1.00-6.73) with normal CRP and 2.40 ng/mL/mg (1.25-6.45) with increased CRP (p = 0.36). For NDCIT, the C/D median actually trended slightly higher with normal CRP *vs* high CRP (1.08 ng/mL/mg and 0.85 ng/mL/mg; p = 0.64), and the metabolic ratio NDCIT/CIT exhibited a similar upward shift (0.45 and 0.33; p = 0.09). It should be noted that the authors underline substantial inter-individual variability across the results [37].

3.2.2. Venlafaxine

Venlafaxine (VEN) is a selective serotonin and Norepinephrine Reuptake Inhibitor (SNRI) that is frequently employed in the treatment of major depressive disorder and related affective disorders. This phenylethylamine derivative acts primarily by inhibiting the reuptake of both 5-HT and norepinephrine transporters in the central nervous system [38]. VEN is extensively metabolised in the liver, mainly *via* the cytochrome P450 isoenzyme CYP2D6. The principal active metabolite is represented by O-desmethylvenlafaxine (ODV). VEN is also metabolised to a lesser extent by CYP2C19 and CYP3A4 to form N-desmethylvenlafaxine [39]. Although both metabolites possess antidepressant activity, ODV is generally considered to be the moiety with higher clinical relevance [38]. In the previously cited study, Hefner *et al*. also assessed a cohort of 39 VEN-treated psychiatric patients (median age 57 years; 46% ≥65 years; 54% female). Four major pharmacokinetic parameters were analysed: dose-corrected VEN C/D, ODV C/D, the C/D of the sum of the two active moieties (VEN + ODV), and the ODV/VEN metabolic ratio. No significant effects of the CRP elevation on the examined parameters were observed. Median C/D for VEN was 0.59 ng/mL/mg (range 0.12-2.25) during the normal CRP state and 0.54 ng/mL/mg (0.11-3.07) during elevated CRP (p = 0.31). For ODV C/D, subjects had a median C/D of 0.95 ng/mL/mg (0.29-3.18) vs 1.06 ng/mL/mg (0.32-3.19); (p = 0.12), respectively. For the sum of active moieties, a median C/D of 1.68 ng/mL/mg (0.59-3.94) *vs*. 1.76 ng/mL/mg (0.71-4.15); (p = 0.09), respectively. The ODV/VEN metabolic ratio also appeared to be stable between conditions [1.77 (0.25-11.51) *vs*. 2.32 (0.23-12.68); p = 0.78] [37].

3.3. Inflammation and Antipsychotics Pharmacokinetics

3.3.1. Clozapine

Clozapine (CZP) is a Second-Generation Antipsychotic (SGA) primarily indicated for treatment-resistant schizophrenia and for reducing the risk of recurrent suicidal behaviour in schizophrenic patients. It exerts its effects by antagonizing dopaminergic (D2) and serotonergic (5-HT2A) receptors, with significant affinity for multiple other neurotransmitter receptors [40]. CZP is extensively metabolized in the liver, mainly by CYP1A2, with minor contributions from CYP2C19, CYP3A4, and CYP2D6 [41]. Its principal metabolite, norclozapine (desmethylclozapine, NCZP), lacked antipsychotic activity when tested, but it can contribute to the side-effect profile, whereas other metabolites are considered less clinically relevant [42]. Considering anecdotal sources, several case reports have documented changes in CZP metabolism in elevated CRP conditions. In a case described by Buist & Schauer, a 57-year-old woman, while being titrated to 300 mg/day, developed fever (39.5°C) and a CRP surge to 211 mg/L. The CZP measured level, spiked from the therapeutic range to 3280 nmol/L [43]. Another case, reported by Espnes *et al*., described a 23-year-old man on a CZP dose of 900 mg/day. In this case, the onset of a bacterial gastro-enteritis was observed (CRP 130 mg L^{-1}). The inflammatory condition drove the CZP level to 9074 nmol/L; however, the symptoms were mild [44]. Another case reported by Farha *et al*. examined a 44-year-old male. In this case, a value of CRP equal to 130 mg/L coincided with a CZP level of 1301 μg/L. Furthermore, an NCZP/CZP ratio collapse to 0.4 was also observed [45]. Ruan et al. prospectively followed two patients. Both were treated with clozapine at doses ranging between 200 and 375 mg/day. Inflammation increased the C/D by 45% and 133%, respectively [46]. Leung *et al*. also reported a series of three cases involving adult patients (ages 32, 42, and 52; two males and one female). These patients were on maintenance CZP therapy (200 to 800 mg/day) and developed severe infectious/inflammatory episodes. In each instance, there was a rapid rise in serum CZP levels, and the CZP/NCZP ratio was increased from standard values to up to 8.6:1 (normal ~2:1) [47]. Shelton and colleagues also reported a series of three cases. The patients were aged between 19 and 23 years, experiencing their first episode of psychosis, and undergoing CZP initiation. During the titration phase, all three patients developed significant inflammatory responses, with CRP values rising to as high as 37 mg/L. Doses ranging from 50 mg/day to 125 mg/day were sufficient to achieve plasma concentrations of CZP >350 ng/mL [48]. Arrojo-Romero and colleagues reported a case series of six long-term inpatients who developed COVID-19 while on CZP treatment. In four patients, C/D ratios remained within a mild to moderate range (0.7-2.5 ng/mL per mg/day) and did not require dosage adjustments, whereas in two cases with marked systemic inflammation (CRP elevations and pneumonia) the C/D ratio rose to >3, necessitating a reduction of the daily dose by 50% and 33%, respectively [49].

Considering observational studies, Ruan and colleagues retrospectively evaluated 134 CZP-treated patients. Among those, 16 individuals had 18 episodes of infection associated

with marked increases in the CZP C/D ratios. Mean C/D values ranged approximately from 1.5-2.5 ng/mL per mg/day in the absence of infection to 3-6 ng/mL per mg/day during infection [50]. Hefner *et al*. conducted an intra-individual TDM study on 33 adult patients (15 women, 18 men; median age 40 years, range 24-79). For all patients, two steady-state samples were collected. One with CRP <5 mg/L, and the other with CRP ≥5 mg/L. The results showed that when comparing the two conditions, a significant increase in the median CZP C/D ratio was observed (1.15 ng/mL/mg vs 1.81 ng/mL/mg; +48%; $p < 0.01$). In addition to that, the metabolic ratio of NCZP/CZP decreased from 0.58 to 0.47 ($p = 0.013$) [25]. In another study, Smith *et al*. conducted a retrospective evaluation of TDM samples of 60 CZP-treated inpatients. Samples were stratified both in accordance with the observed CRP level and the smoking status of the patient. Among non-smokers, the results showed a more than three-fold increase in the CZP C/D ratio in patients with high CRP levels (>50 mg/L) [51].

3.3.2. Olanzapine

Olanzapine (OLA) is an SGA for schizophrenia and bipolar disorder. Its mechanism of action involves antagonism at multiple neurotransmitter receptors, particularly dopamine D2 and serotonin 5-HT2A receptors [52]. OLA is metabolised in the liver mainly by CYP1A2 and UGT1A4, and to a lesser extent by CYP2D6. The principal metabolites, including 10-N-glucuronide and N-desmethylolanzapine, are largely inactive, and OLA's therapeutic effects are primarily due to the parent compound [53]. For OLA, the only currently available evidence comes from a multi-drug TDM study by Scherf-Clavel *et al*., focusing on patients with pathological CRP (≥5 mg/L). The study population covered a spectrum of psychiatric diagnoses, as TDM was requested in routine clinical care. The OLA cohort consisted of 24 adult patients (12 women, 12 men; mean age = 47.7 ± 17.7 standard deviation (SD)). Daily OLA doses ranged from 0.5 mg/day to 20 mg/day. Mean CRP was 19.1 mg/L ± 1.92 SD (range: 5.1-76.1 mg/L). Statistical analysis showed a trend toward a positive relationship between CRP and dose-adjusted OLA concentrations; however, no statistical significance was observed (Spearman r = 0.385, $p = 0.063$; linear regression $p = 0.086$). No significant difference in CRP levels or leukocyte count was observed between patients with serum OLA concentrations above or below the upper therapeutic threshold of 80 ng/mL. Neither variable emerged as a significant predictor in the regression models [54].

3.3.3. Quetiapine

Quetiapine (QUE) is an SGA indicated for the treatment of schizophrenia, bipolar disorder, and as adjunct therapy in major depressive disorder. Its therapeutic effects are attributed to antagonism of 5-HT2A and D2 receptors, among others [55]. QUE undergoes extensive hepatic metabolism primarily *via* CYP3A4, leading to the formation of its main active metabolite, norquetiapine (N-desalkylquetiapine, NQUE) [56]. NQUE exhibits pharmacological activity, including norepinephrine reuptake inhibition, which may contribute to the clinical profile of QUE [57]. The previously cited study by Scherf-Clavel and colleagues also analysed a cohort of QUE-treated patients. The analysis encompassed 166 samples from patients treated with QUE (98 women, 68 men; mean age = 50.5 ± 16.3 SD). The mean daily dose was 337 mg/day (range: 50-1200 mg/day). The Spearman correlation coefficient between CRP and C/D ratio for QUE was r = 0.269 ($p < 0.001$), indicating a positive association between CRP level and QUE exposure. The mean C/D rose from 0.56 ± 0.53 (ng/mL)/(mg/day) in the lowest CRP group (0.5-1.0 mg/dL) to 0.89 ± 0.84 (ng/mL)/(mg/day) in patients with CRP values exceeding 5 mg/dL. Furthermore, among the 166 individuals studied, 14 (8.4%) had serum concentrations exceeding 500 ng/mL. The observed median CRP value in this subgroup was significantly higher than in patients with lower CRP concentrations (2.90 *vs*. 1.58 mg/dL, $p=0.006$) [54]. The aforementioned study by Hefner *et al*. also systematically assessed QUE in a cohort of 32 adult patients (15 women, 17 men; median age 41 years, range 25-74). The study found that the median dose-corrected QUE C/D ratio increased from 0.34 to 0.40 ng/mL/mg (+11.9%), but this difference did not reach statistical significance ($p = 0.053$). The NQUE/QUE metabolic ratio decreased from 1.70 to 1.24, but this change was also not statistically significant ($p = 0.484$) [25].

3.3.4. Risperidone

RIS is an SGA used in the treatment of schizophrenia, bipolar disorder, and irritability associated with autism. It acts mainly by antagonising dopamine D2 and serotonin 5-HT2A receptors [58]. RIS is metabolised hepatically by CYP2D6 and, to a lesser extent, by CYP3A4 to paliperidone (9-hydroxyrisperidone, PAL), its primary active metabolite. Both RIS and PAL contribute significantly to the drug's pharmacological and clinical effects [59]. Scherf-Clavel and colleagues also evaluated a cohort of 45 RIS-treated patients (25 women, 20 men: mean age = 48.5 years ± 12.2 SD) with doses ranging from 0.5 to 8 mg/day. No statistically significant association between pathological CRP (≥0.5 mg/dL, mean = 1.74 mg/dL ± 1.72 SD) and RIS plasma concentrations was observed in either raw or dose-normalised specifications. No meaningful difference was observed between patients who were above *vs*. below the 60 ng/mL active moiety threshold, or in regression models controlling for age, sex, and dose [54]. A less numerous cohort of 40 adult RIS-treated patients (18 women, 22 men; median age 44 years) with severe psychiatric illness was also present in the study by Hefner. In this case, the median dose-corrected active moiety concentration (RIS + PAL) increased significantly from 8.0 to 10.2 ng/mL/mg (+24.2%, $p = 0.003$) during periods of inflammation. The metabolic ratio (PAL/RIS) remained stable (from 5.71 to 5.71, $p = 0.250$) [25]. Hefner *et al*. also reported two clinical cases. Both involved female patients (aged 56 and 38 years) were in maintenance treatment with RIS at a dosage of 6 mg/day. The two developed acute infections accompanied by extremely elevated CRP values (105 and 110 mg/L). In both cases, C/D ratios exceeded the "clearance impaired" threshold of 14 ng/mL/mg as defined by de Leon *et al*., indicating severely compromised drug elimination [60]. The authors also observed that the metabolite/parent ratio (PAL/RIS) remained stable throughout the observation period. Despite the marked increases in RIS active moiety, no severe neurological adverse effects were observed. The only clinically relevant side effect reported was rigidity in one patient during a recurrence of pneumonia [61]. Helland and colleagues also described a

clinical case in which a 56-year-old man with schizophrenia was in chronic treatment with RIS (8 mg/day), exhibiting stable active moiety concentration (98 nmol/L). During an acute episode of severe inflammation (atypical pneumonia, CRP 30 mg/L), total active moiety concentrations increased to 405 nmol/L. After the RIS dose was reduced in response to these elevated levels, the patient experienced a relapse of psychotic symptoms, despite "therapeutic" total concentrations [62].

3.3.5. Aripiprazole

Aripiprazole (ARI) is a third-generation atypical antipsychotic (TGA) approved for schizophrenia, bipolar disorder, and as adjunctive treatment for major depressive disorder. It acts as a partial agonist at dopamine D2 and serotonin 5-HT1A receptors and as an antagonist at 5-HT2A receptors [63]. ARI is metabolised mainly *via* CYP2D6 and CYP3A4, yielding the active metabolite dehydroaripiprazole [64]. This metabolite possesses similar pharmacological properties and contributes significantly to the clinical activity of ARI [65]. For ARI, the same study by Scherf-Clavel *et al*. represents the only source of information. The cohort in this case included 30 adult patients (20 women, 10 men; mean age = 44.5 years, ± 15.2 SD). The mean CRP was 1.70 mg/dL (± 2.60 SD). CRP values ranged from 0.51 mg/dL to 14.58 mg/dL. Daily doses of ARI varied from 5 mg to 30 mg with a mean serum concentration value of 254.5 ng/mL (± 177.9 SD). Statistical analysis revealed no significant correlation between CRP and dose-corrected ARI concentrations ($p = 0.44$) [54].

4. DISCUSSION

4.1. Inflammation and Antidepressants Pharmacokinetics

The limited available evidence for antidepressants points towards a lack of significant impact of inflammation on the pharmacokinetics of both CIT and VEN. This might appear puzzling at first, as pro-inflammatory cytokines such as IL-1β and IL-6 can downregulate the transcription and activity of major CYP isoforms involved in antidepressant metabolism [66, 67]. Indeed, the action of these inflammatory cytokines could convert genetically extensive metabolizers into functional poor metabolizers, in a phenomenon called phenoconversion [66, 68]. This should, in theory, lead to inflammation-driven changes in antidepressant plasma levels.

However, a factor to consider in this context is the isoform-specific sensitivity of CYP450 to inflammation. IL-6, IL-1β, and TNF-α consistently exert their most substantial downregulatory effects on CYP3A4, CYP2C19, and CYP2C9; CYP1A2 falls in a similar moderate range, whereas CYP2D6 is the least susceptible [66]. This is particularly important for VEN, which is mainly metabolised by CYP2D6, as in poor metabolizers, its clearance could be more reliant on alternative pathways, particularly N-demethylation by CYP3A4 [69]. Thus, in individuals with this phenotype, the effects of systemic inflammation on the pharmacokinetics of VEN could be amplified. Differences in phenotypic expression of CYP enzymes are also a recognised source of variation in pharmacokinetic response [69]. Inter-individual variability in CYP function may also have overshadowed or masked potential inflammation effects on pharmacokinetics [70]. Drug clearance rates and steady-state serum concentrations may differ several-fold between individuals, even under otherwise standardised conditions [71-73]. Furthermore, non-genetic factors, the accounting of which is made impossible by the single available data source, could also be at play. Indeed, concomitant medications, inflammation, and hormonal status could further modulate CYP activity, resulting in additional pharmacokinetic variability [69, 74].

In addition to that, several antidepressants have demonstrated intrinsic anti-inflammatory properties. In a meta-analysis of six clinical trials, antidepressant therapies were associated with a robust reduction in serum IL-1β concentrations (standardised mean difference (SMD) = −0.52; 95% CI −0.83 to −0.20; Z = 3.23; $p = 0.001$). Furthermore, in the same analysis, SSRI monotherapy was associated with a marked decrease in serum IL-6 concentrations [26]. This could, in theory, create a hypothetical scenario in which cytokine suppression by SSRIs such as CIT and inflammation-driven reductions in clearance may counterbalance each other.

4.1.1. Mechanistic Considerations and Clinical Implications

The complex relationship between the anti-inflammatory effects of certain antidepressants and the inflammation-mediated regulation of CYP enzymes raises questions around the clinical stability of SSRI pharmacokinetics in inflammatory contexts. As previously stated, medications such as CIT could theoretically downregulate the production of pro-inflammatory cytokines, thereby preventing CYP isoform suppression. Through this hypothetical feedback mechanism, the immunomodulatory effects of some SSRIs might theoretically reduce the effects of systemic inflammation. However, this hypothesis remains highly speculative as there are, to the best of our knowledge, currently no experimental or clinical evidence exploring these aspects. In addition to that, the anti-inflammatory effects of SSRIs cannot be assumed to be consistent across the drug class, as pointed out by the literature [75].

Another reason for caution in this context is that antidepressants primarily metabolised by inflammation-sensitive CYP isoforms but lacking intrinsic cytokine-modulating activity might be more vulnerable to inflammation-induced pharmacokinetic alterations [76, 77]. Yet, to the best of our knowledge, no clinical studies have systematically evaluated this scenario to date.

Finally, it is also important to highlight the significant methodological concerns regarding the available evidence. The only evidence source had a small sample size, particularly for the CIT cohort, which strongly impedes the drawing of firm conclusions. Furthermore, various other potential sources of variability were also present [78], but lacked a proper assessment.

Given these knowledge gaps, there is an evident need for carefully designed, prospective cohort studies aimed at understanding the pharmacokinetic consequences of systemic inflammation on the different antidepressants. Such studies should also include pharmacogenetics, immunological sampling and profiling, as well as in-depth definitions of the inflammatory status, to provide a more robust evidence base to evaluate this complex phenomenon.

4.2. Inflammation and Antipsychotics Pharmacokinetics

4.2.1. Clozapine

The data regarding CZP are the most robust among those available for antipsychotics, suggesting an overall coherent picture. CZP metabolism appears to be significantly influenced by inflammatory states. This matches its metabolic reliance mainly on the hepatic isoenzyme CYP1A2 for clearance [79]. As previously mentioned, CYP1A2 is prone to down-regulation by pro-inflammatory cytokines, especially IL-6 [66]. Moreover, the association of CRP elevation with increased CZP concentrations only in non-smokers is consistent with the fact that tobacco smoking is a strong inducer of CYP1A2 activity due to polycyclic aromatic hydrocarbons in cigarette smoke [80]. Chronic induction of CYP1A2 in smokers results in an increase of baseline metabolic clearance for CZP in this group and provides some degree of "metabolic buffering" against the inhibitory effects of inflammation-derived cytokines [51]. In this context, smoking may partially offset, or even mask, the suppressive impact of inflammatory states on CYP1A2 activity and CZP metabolism. However, the fact that a CZP titration that is too rapid for a given patient's metabolism can lead to CZP-induced inflammation should also be considered [81]. Indeed, if the CZP dosage is increased during titration, it leads to positive feedback, further increasing cytokine release and subsequently inhibiting CZP metabolism. CZP-induced inflammation can manifest with a wide variety of presentations, including: 1) systemic inflammatory processes: fever, isolated CRP elevation, or lupus; or 2) localised signs of inflammation: myocarditis, serositis, pneumonitis/alveolitis, hepatitis, pancreatitis, nephritis, colitis, and dermatological disorders [81]. Several conditions associated with eosinophilia may also co-occur, including CZP-related *"drug reaction with eosinophilia and systemic symptoms"* (DRESS) syndrome [82]. Indeed, in a few studies of CZP TDM during CZP-induced myocarditis, co-occurring infections were common and likely contributed to the development of CZP-induced myocarditis [83, 84]. These factors justify a proactive, CRP-guided approach to CZP dose adjustment, with expert consensus recommending halving the dose when unexplained CZP levels exceed 1,000 ng/mL, or CRP surpasses 100 mg/L, and only re-escalating therapy after sustained normalisation of inflammatory markers [85].

4.2.2. Olanzapine

As far as OLA is concerned, the available data is extremely limited. Although the trends reported in the only available study hint at a possible effect of inflammation on its pharmacokinetics, the lack of statistical significance prevents any affirmations in this sense. However, it should be noted that, unlike CZP, OLA does not pose an inflammatory response-induction risk during titrations, and OLA-induced myocarditis appears to be extremely rare [86]. Considering this and the fact that CRP elevations do not seem to be a robust predictor of variations in OLA levels, at least in the only available cohort, further investigations are urgently needed.

4.2.3. Quetiapine

QUE-related data seem to indicate a less pronounced and more variable relationship with systemic inflammatory markers. This could be due to the heavy reliance of QUE on CYP3A4 for its metabolism [56]. Indeed, when compared to CYP1A2, the main isoform responsible for the metabolism of CZP, CYP3A4, seems to exhibit a higher interindividual variability [87]. Thus, given the relatively limited number of subjects analysed, the influence of individual variation on the results cannot be underestimated, and further investigation is highly recommended in this case as well.

4.2.4. Risperidone

The available data suggest a certain level of heterogeneity in the impact of inflammation on RIS pharmacokinetics. Indeed, the observation of a stable metabolic ratio in both the study and the case reports by Hefner *et al*. is in line with the supposed marginal effect of inflammation on CYP2D6, the main metabolising enzyme of RIS [88]. This pattern suggests a non-selective reduction in hepatic clearance rather than specific pathway inhibition. This phenomenon is plausibly due mainly to downregulation of CYP3A4 or other non-CYP pathways. Such a mechanism aligns with similar findings in CZP and QUE, highlighting the potential for major pharmacokinetic shifts during acute-phase responses [62]. This is also in line with the observed heterogeneity in exposure increases, plausibly reflecting inter-individual differences in baseline clearance capacity and metabolic background (including CYP2D6 status), particularly under severe acute-phase responses (CRP >100 mg/L). However, the influence of factors such as the different grades of inflammation observed or unmeasured confounders, such as smoking status, could not be ruled out [54, 89].

4.2.5. Aripiprazole

The limited data available for ARI seem to be consistent with its pharmacokinetic profile. Indeed, both the CYP3A4 and CYP2D6 pathways seem to contribute substantially to ARI metabolism [90]. Considering this, the effect of a condition (such as inflammation) that might lead to the suppression or reduction of one metabolic pathway might be compensated for by the activity of the other [91]. Furthermore, the long half-life of ARI (approximately 75 hours) might buffer against rapid or transient changes in drug clearance [92]. These factors point towards a relative stability of the ARI metabolism in inflammatory conditions.

4.2.6. Mechanistic Considerations and Clinical Implications

Based on the current body of evidence available for antipsychotics, some considerations could be drawn. The time course of increases in dose-normalised drug levels relative to increases in CRP points to the need for more dynamic, inflammation-sensitive monitoring. Strong evidence that supports the reduction of the CZP dose by half when CRP exceeds 100 mg/L. The same should be applied when total serum concentrations exceed 1,000 ng/mL. Then the dose should be carefully re-escalated until inflammatory markers return to normal [85]. For QUE and RIS, a 25-50% dose reduction is generally advised if the C/D doubles from baseline in the context of elevated CRP [54]. Measurement of CRP remains highly suggested when unexpectedly high drug levels are observed. The same remains advisable if patients experience clinical deterioration without apparent reasons [93].

Another aspect to treat with caution is the interpretation of TDM. In fact, acute-phase protein binding, such as with the α1-acid glycoprotein (AGP), should be contemplated as a potential factor impacting total plasma drug concentrations. With a rise in AGP levels, typical of an inflammatory status, a higher proportion of the circulating drug will bind to AGP [94, 95]. Most routine laboratory assays measure only the total drug concentration. However, if AGP sequesters more of the drug, the total measured concentration of the drug may increase, but the free (active) drug concentrations that exert pharmacologic effects may remain steady [96]. This dynamic can produce a disconnect between laboratory results and clinical effects. Thus, patients may be displaying very high plasma drug levels without manifesting severe toxicity. Such a phenomenon has been observed in CZP and RIS-related clinical cases [44, 62].

The risk of pharmacokinetic interactions from co-administered medications should also be considered. Concomitant use of other drugs, particularly those that can inhibit or induce CYP enzymes, may further affect antipsychotic metabolism during inflammatory states.

4.3. Future Perspectives

Considering the complexity of the examined evidence, this paragraph will be divided into a general recommendation section for antidepressants/antipsychotics and a specific section for future developments on the clozapine-inflammation relationship topic.

4.3.1. General Recommendations

The complex relationship between systemic inflammation and pharmacokinetics, detailed throughout this review, illustrates a clinical and biological landscape that could be regarded as highly variable. Factors influencing the inflammatory response, such as genetics, metabolic pathways, and psychosocial/environmental exposures, all interact to create variation in both safety and efficacy in patients treated with an antipsychotic or antidepressant. In this context, interdisciplinary collaboration among psychiatrists, clinical pharmacologists, and laboratory medicine specialists becomes essential [97]. The joint development of protocols for monitoring, dose adjustment, and follow-up in patients with comorbid infections or inflammatory conditions is a critical step forward [98]. Future studies should include a comprehensive consideration of several aspects, including pharmacogenetics testing and drug-drug interactions. Furthermore, the use of data science techniques, such as machine learning, would be beneficial for analyzing complex, rapidly growing datasets [99, 100]. Additionally, the discovery and validation of actionable biomarkers could improve the identification of at-risk patients and personalised drug selection and dosing, thereby facilitating precision psychiatry.

4.3.2. Clozapine Recommendations

CZP has a very complex relationship with inflammation and infection [101]. Thus, in our opinion, subsequent studies should investigate this topic from different perspectives. Current international guidelines on CZP titration practice propose measuring CRP during titration to prevent CZP-induced inflammations [85]. However, CRP levels can be increased by both CZP-induced inflammation and concomitant infection. Therefore, other possible markers should be considered. Kluge and colleagues found that the CZP-induced fever was particularly associated with IL-6 peak levels that were not present in OLA-treated patients [102]. Thus, further studies on the role of IL-6 as a possible marker of CZP-induced inflammation could be of relevance [103]. Two recent studies have explored a new index of inflammation during CZP titrations; this index is known as the neutrophil-to-lymphocyte ratio (NLR) [104, 105]. Currently, the NLR is widely used across many medical disciplines, including emergency medicine, cancer, and perioperative medicine [106]. The NLR monitoring seems to be particularly suitable for CZP titration, as white blood cell (WBC) counts are measured to rule out agranulocytosis [104]. Furthermore, the CZP titrations developed in the United States (US) are not appropriate for patients of Asian ancestry, as they have lower CZP clearance [107]. Thus, the NLR may be very helpful in any country in which the practised titrations are not personalised for ancestry [108, 109]. In our opinion, NLR should be studied as a marker of inflammation and compared with CRP in patients taking other antipsychotics than CZP or antidepressants. Moreover, based on the findings by Smith *et al*. [51], smokers may be at a lower risk of inflammation-related clozapine intoxication. Nevertheless, given the limited available evidence, further investigation is warranted.

4.4. Strengths and Methodological Limitations

To the best of our knowledge, this review is the first to provide an evaluation of the evidence regarding the influence of inflammation on the pharmacokinetics of both antidepressants and antipsychotics. In addition to the previously discussed issues regarding the quality of available data, limitations inherent to the review process are also present. The number of eligible studies for this review was low; for antidepressants, only one study met our inclusion criteria, severely limiting our capacity to draw firm conclusions. Furthermore, there were significant differences across studies in study design, populations studied, and reporting methods. Due to these characteristics, it was not possible to use any synthetic or quantitative methods (*e.g*., meta-analyses or meta-regressions); thus, a narrative presentation of the data was adopted. The lack of a prior registration of the review protocol to a systematic review registry (*e.g*., PROSPERO) also represents a limitation; nevertheless, the PRISMA 2020 guidelines were followed. Finally, relevant unpublished data, grey literature, or studies indexed in non-English databases may have been missed, introducing potential publication/language biases.

CONCLUSION

Recognition of the relationship between systemic inflammation and the pharmacokinetics of psychiatric medications is beginning to gain momentum clinically, especially in relation to antipsychotics. These phenomena may potentially increase the risk of concentration-dependent adverse effects and should be considered when developing individual management plans. Nevertheless, the current evidence base is very limited, especially for antidepressants, and is plagued by several limitations. Therefore, the necessity for larger

prospective studies remains pressing. Potentially acting on increased demands for more thorough assessments of inflammatory status in psychiatric patients as part of routine clinical care may represent an initial step towards a more personalised, safer, and effective treatment.

AUTHORS' CONTRIBUTIONS

The authors confirm their contributions to the paper as follows: ES, GS, JdL, and AC contributed to conceptualization; AG and NC handled data curation and methodology; GC and MAB conducted the investigation; ES, FB, MG, and JdL performed validation; GC and LS were responsible for visualization; GC and MAB prepared the original draft; and AC, ES, JdL, and GS contributed to writing-review and editing. All authors reviewed and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

5-HT	=	5-Hydroxytryptamine (Serotonin)
AD	=	Antidepressants
AGP	=	Alpha-1-Acid Glycoprotein
AP	=	Antipsychotics
ARI	=	Aripiprazole
C/D	=	Concentration-To-Dose Ratio
CIT	=	Citalopram
CNS	=	Central Nervous System
CRP	=	C-Reactive Protein
CZP	=	Clozapine
FEP	=	First-Episode Psychosis
IL-1β	=	Interleukin-1 Beta
IL-6	=	Interleukin-6
MDD	=	Major Depressive Disorder
MR	=	Metabolic Ratio
NCZP	=	Norclozapine (Desmethylclozapine)
NDCIT	=	N-Desmethylcitalopram
NQUE	=	Norquetiapine (N-Desalkylquetiapine)
ODV	=	O-Desmethylvenlafaxine
OLA	=	Olanzapine
PAL	=	Paliperidone (9-Hydroxyrisperidone)
PK	=	Pharmacokinetic
PM	=	Poor Metabolizer
QUE	=	Quetiapine
RIS	=	Risperidone
SNRIs	=	Serotonin-Norepinephrine Reuptake Inhibitors
SSRIs	=	Selective Serotonin Reuptake Inhibitors
SzA	=	Schizoaffective Disorder
TDM	=	Therapeutic Drug Monitoring
TNF-α	=	Tumor Necrosis Factor-Alpha
TRD	=	Treatment-Resistant Depression
VEN	=	Venlafaxine
WOS	=	Web Of Science

CONSENT FOR PUBLICATION

Not applicable.

STANDARD OF REPORTING

PRISMA guidelines and methodology were followed.

AVAILABILITY OF DATA AND MATERIALS

All the data and supportive information are provided within the article.

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CONFLICT OF INTEREST

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Declared none.

SUPPLEMENTARY MATERIAL

The supplementary material attached to this paper includes two boxes detailing the research strategy used and three tables (Supplementary Tables **1**-**3**) presenting the results. Of the risk of bias assessment and two tables (Supplementary Tables **4**, **5**) presenting the percentage changes in antidepressant and antipsychotic C/D ratios.

PRISMA checklist is available as supplementary material on the publisher's website. Supplementary material is available on the publisher's website along with the published article.

PROTOCOL REGISTRATION AND DATA AVAILABILITY

The present review was not registered before submission. The research protocol was not formally submitted before the submission of the present paper. Data sources, except for PubMed and Google Scholar, were consulted under licence

agreements between the University of Messina and the owners of the respective databases.

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