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REVIEW

Increased Interleukins: Effect of Risperidone in Individuals with Schizophrenia—a Systematic Review

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Abstract

Atypical antipsychotic drugs such risperidone are selected for the first-line treatment of individuals with schizophrenia. In this sense, it has been observed that when risperidone is used frequently, it can induce changes in metabolism, which could alter pro-inflammatory cytokine levels. The aim of this systematic review was to evaluate the role of risperidone in interleukin levels of individuals with schizophrenia. The systematic search was performed in PubMed, Scopus, and EBSCO databases up to March 2023. Interleukin levels were evaluated in individuals with schizophrenia before and after treatment with risperidone and also compared with control groups. The most common interleukins analyzed before and after treatment with risperidone were IL-6, IL-17A, IL-10, IL-4, IL-2, IL-1B, and IL-8. With regard to case-control studies, we observed that the main interleukins evaluated were IL-2, IL-6, IL-1B, IL-12, IL-10, IL-4, and IL-8. Evidence indicates that individuals with schizophrenia who undergo a regular treatment with risperidone could trigger the release and circulation of pro-inflammatory interleukins and therefore, their concentration in plasma or serum increases. More studies are needed to evaluate more variables.

Keywords Interleukins · Serum · Schizophrenia · Risperidone

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Introduction

Atypical antipsychotic drugs are regularly selected as the first-line treatment of individuals with psychiatric disorders including schizophrenia [1–3]. Risperidone for instance, also named Risperdal, is classified as an atypical second-generation antipsychotic that has an antagonistic role on 5-hydroxytryptamine (5-HT) 2A and D2 dopamine receptors; [1, 4] although it is highly used for treating individuals with schizophrenia, risperidone can induce important changes such as metabolic syndrome [5, 6]. Changes in pro-inflammatory cytokine concentrations have also been reported when using this drug, increasing [7–9] or decreasing cytokine levels, and the inflammatory process has been related to metabolism alterations [10–13]. Several factors have been proposed to explain the different alterations observed in cytokine levels after risperidone treatment, but no conclusive outcomes have been reached [9, 14].

There are some previous reviews that addressed risperidone treatment in patients with schizophrenia, from studies

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performed in pediatric and adolescents [15] to its pharmacology and therapeutic use [16]. Nevertheless, antipsychotics have a variety of effects on cytokine levels, which main theories are unclear yet. For example, in in vitro studies, risperidone exhibited stimulatory effects on the proinflammatory responses of peripheral cells [17]. Furthermore, it has been reported to increase the levels of anti-inflammatory cytokines in immune-challenged peripheral blood mononuclear cells [18]. On the other hand, in in vivo studies in rodents, risperidone decreases pro-inflammatory cytokine levels in peripheral and central samples [19]. Therefore, it plausibly indicates that risperidone is able to modulate inflammatory response. In this way, in patients with schizophrenia, serum levels of cytokines (e.g., TNF-α, IL-1β, and IL-6) were significantly higher before risperidone treatment than the healthy controls or after treatment [10]. Additionally, a group of patients with first-episode psychosis presented higher IL-6, IL-10, and TNF-α levels. However, after risperidone treatment, these three cytokines and meanwhile IL-4 decreased significantly [20].

Moreover, there are some reports that address the association of interleukin levels and antipsychotic treatment [21, 22]. Nevertheless, to our knowledge, there are no systematic reviews evaluating risperidone treatment per se among a wide spectrum of cytokine levels in patients with schizophrenia. Consequently, we aimed to perform a systematic review to assess IL-17A, IL-10, IL-4, IL-2, IL-1B, IL-8, and IL-6 levels in patients with schizophrenia under risperidone treatment.

Material and Methods

The protocol was registered in the international database of prospectively registered systematic reviews, PROSPERO, registration number: CRD42021246974.

Literature Search Strategy

The search was performed by two members of our team, both of whom searched independently; literature search was carried out until March 2023. We systematically search for relevant publications using PubMed, EBSCO, Web of Science, and Scopus databases. The terms used to maximize the following terms were used: (“risperidone” OR “risperidal”) AND (“interleukin*” OR “cytokine*” OR “IL-1” OR “IL-1β” OR “IL-2” OR “IL-4” OR “IL-6” OR “IL-8” OR “IL-10” OR “IL-17A”. We also examined the reference lists of the articles for additional relevant studies that were not identified at first. Furthermore, references from association reviews of interleukins and antipsychotics were checked. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria were used to carry out this work.

Study Selection Criteria

All the selected studies were analyzed by two reviewers according to the titles and abstracts. To resolve disagreements, a consensus was reached with a third reviewer. Duplicate literature was removed and all relevant studies were fully read and selected by following the established eligibility criteria. The following elements were used for the selection of studies: (1) purpose: association of interleukin levels and risperidone; (2) population: studies with a group diagnosed with schizophrenia, if the study included a group with any other psychiatric disorder only was take in consideration data from schizophrenia; (3) design: studies evaluating interleukin level before and after risperidone treatment or studies evaluating interleukin levels in patients with schizophrenia (cases) and healthy individuals (controls); (4) outcome variables for qualitative synthesis: to report the different concentrations of interleukin levels before and after risperidone treatment and between cases and control groups; and (5) literature search: articles published in index pairs of peer-reviewed journals (e.g., JCR, Clarivate Web of Science).

Exclusion criteria were (1) sort of publications other than original articles (e.g., reviews, abstract from conferences, correspondence, or duplicate publications) and (2) studies that employed an antipsychotic other than risperidone.

Data Extraction

From articles that were considered eligible, the following information was extracted: (1) name of first author, (2) year of publication, (3) country of origin, (4) number of participants, (5) mean age of participants, (6) diagnosis, (7) type of treatment, (8) duration of treatment, (9) means and standard deviations of cytokine levels, (10) biological sample, (11) duration of the risperidone treatment, and (12) body mass index. In particular cases where any of the aforementioned points was missing, we contacted the authors to request the information.

Risk Bias and Quality Assessment

The quality of the studies was assessed using the Newcastle-Ottawa Scale (NOS). A range of zero to nine was assigned to each item. The studies obtained a score more than 6. Furthermore, we used ROBINS-I tool for evaluation of quality and risk bias (Fig. 1). No studies were excluded because of weakness of design or lack of data quality. We conducted a sensitivity analysis to explore the potential effect of each study on the overall conclusion.

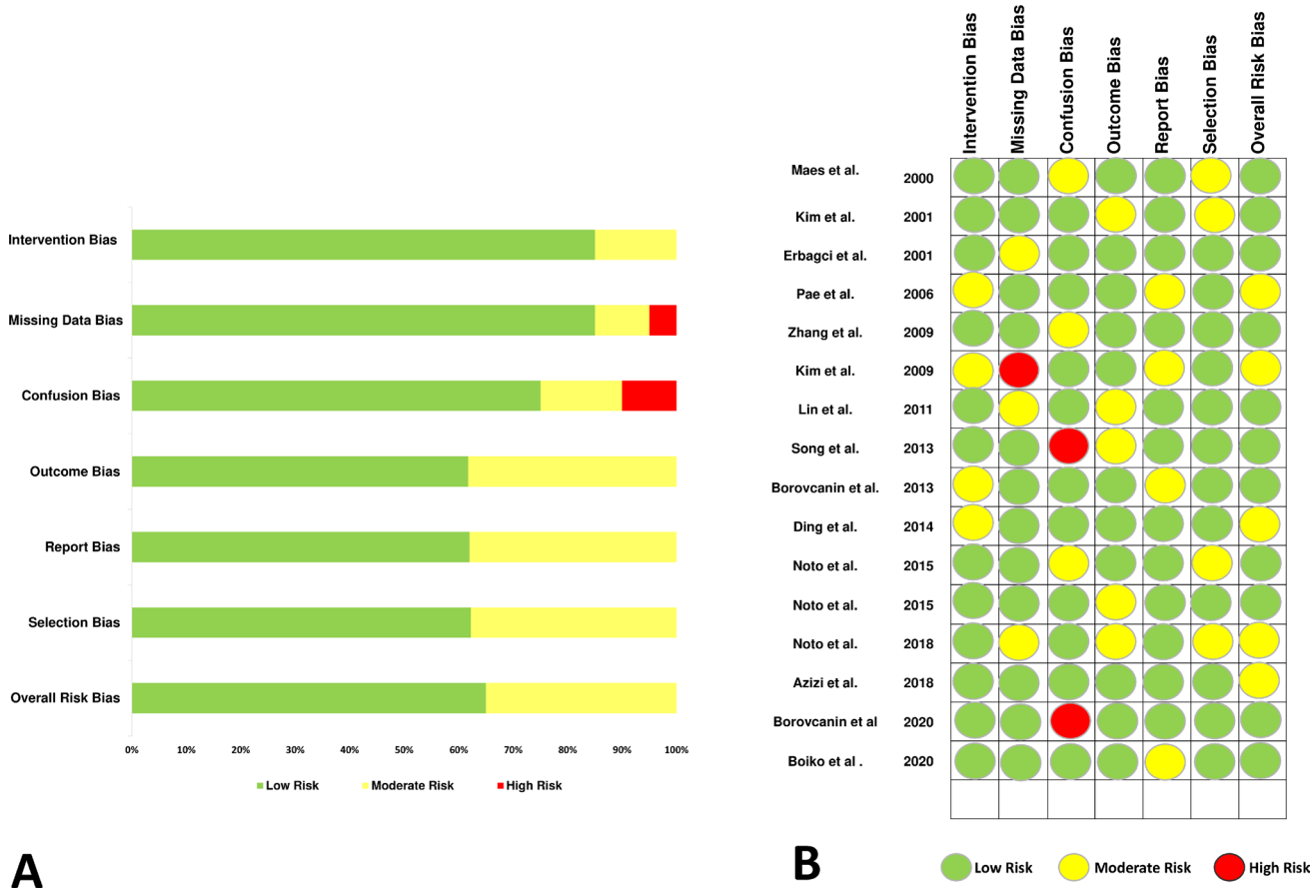

Fig. 1 ROBINS-I tool. **A** Methodological quality graph. **B** Detailed quality assessment with Cochrane risk of bias tool

Results

Identification of Studies

The initial search (in PubMed, EBSCO, Web of Science, and Scopus databases) gave a total of 1597 documents. After excluding duplicates, we reviewed the title of 1455 studies and then excluded those that were not relevant. Forty-five abstracts were considered relevant; 29 full texts were read while systematic reviews and meta-analyses were discarded. Finally, the quantitative synthesis included 17 studies (Fig. 2).

Characteristics of the Included Studies

The publication dates of the selected articles ranged between 2001 and 2021. Sixteen articles were reviewed in total; their main characteristics are detailed in Tables 1 and 2. Subsequently, we analyzed the studies that evaluated the concentrations of IL-6 (17 studies), IL-17A (7 studies), IL-10 (5 studies), IL-4 (5 studies), IL-2 (7 studies), IL-1B (6 studies), and IL-8 (4 studies) in serum or plasma samples in individuals diagnosed with schizophrenia, giving a total of 863 cases and 659 healthy controls. Four studies were conducted in Europe (Serbia = 2, Italy = 1, Turkey = 1, Russia=1); three studies in America (Brazil = 3); while nine studies were from Asia (China = 3, South Korea = 3, Taiwan = 2, Iran = 1) (Table 3). Regarding the laboratory methods (interleukin concentration levels), they included immunoassay systems, immunohistochemistry, and flow cytometry. The interleukins studied were IL-6, IL-17A, IL-10, IL-4, IL-2, IL-1B, and IL-8. In the 17 included studies, we observed that the mean age in the cases was 31.41 ± 8.64 years, while in controls, it was 31.37 ± 7.83 years. The mean BMI in cases was 22.52 ± 3.74 kg/m^2 and 21.66 ± 2.62 kg/m^2 in controls. The samples used were serum and plasma.

Cytokine Levels in Pre-Post–Risperidone Treatment Studies

One way of evaluating the effect of risperidone and cytokine levels is the pre- and post-treatment assessment. Our analysis included studies that evaluated IL-17A levels in a group of individuals with schizophrenia before and after treatment with risperidone. A decrease of IL-17A

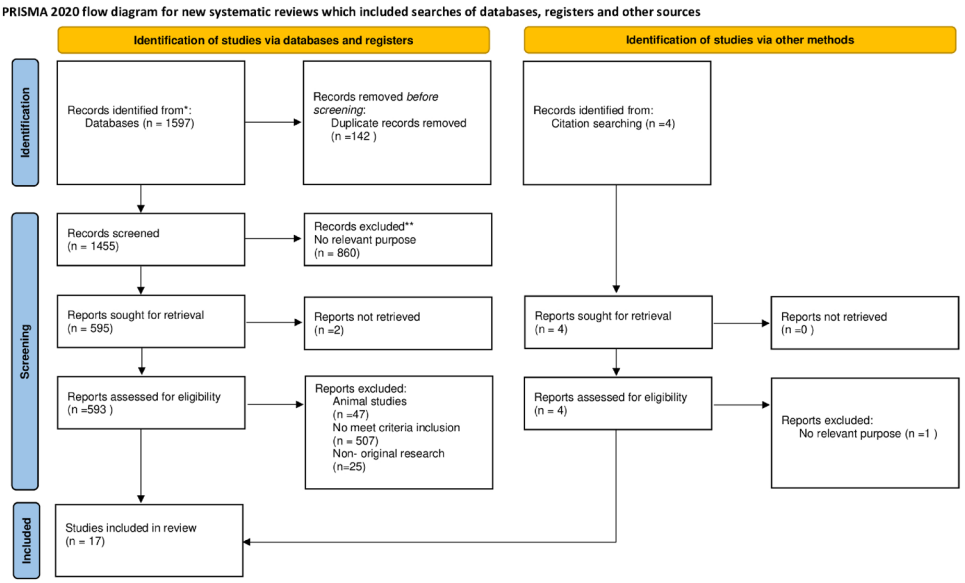

Fig. 2. Flowchart of the systematic review selection criteria

levels was observed after treatment in the schizophrenia group [11, 12]; similarly, an increase of IL-17A levels after treatment was observed in the schizophrenia group [20]. In schizophrenia individuals, regarding the effect of risperidone on IL-10 concentrations, decreased levels were observed after treatment [12, 20]; on the contrary, elevated levels were observed after treatment [23]. On the other hand, a decrease of IL-4 levels was observed in all the studies that evaluated this interleukin [12, 20, 24, 25] after treatment with risperidone. In the same way, a decrease of IL-2 levels after treatment with risperidone was reported [7, 12, 26]. However, elevated levels of IL-2 were found in

Table 1 Summary of the principal characteristics of the studies included

First author	Country	Sample size	Mean age	Gender (M/F)	Evaluation method	Biological sample	Treatment (time/dosage)
Zhang et al. 2009	China	41	43.8	30/11	ELISA	Serum	12 weeks/6 mg/day
Azizi et al. 2018	Iran	24	34.12	17/7	ELISA	Serum	3 months/5 mg/day
Erbagci et al. 2001	Turkey	34	33.1	15/19	Chemiluminescence immunometric	Serum	8 weeks/4 mg/day
Borovcanin et al. 2013	Serbia	27	36.18	16/11	ELISA	Serum	NA
Ding et al. 2014	China	69	27.48	37/32	ELISA	Plasma	2 to 6 mg/day
Kim et al. 2001	South Korea	19	28.4	11/8	ELISA	Serum	4 weeks/2 to 6 mg/day
Noto et al. 2015	Brazil	174	26.19	108/66	Flow cytometry	Serum	4 mg/day
Noto et al. 2015	Brazil	31	25.8	19/12	ELISA	Serum	2 to 6 mg/day
Noto et al. 2018	Brazil	54	24.75	35/19	Flow cytometry	Serum	2 to 6 mg/day
Song et al. 2013	China	62	24.7	29/33	ELISA	Serum	24 weeks/2 to 6 mg/day
Lin et al. 2011	Taiwan	34	34.65		ELISA	Serum	3 to 5 mg/day
Kim et al. 2009	Sur of Korea	71	33.9	32/39	ELISA	Plasma	4 to 12 mg/day
Maes et al. 2000	Italy	14			ELISA	Serum	NA
Pae et al. 2006	Sur of Korea	35	37.7	21/14	ELISA	Serum	NA
Borovcanin et al. 2020	Serbia	53	33.64	36/17	ELISA	Serum	NA
Borovcanin et al. 2013	Serbia	80	35.95	52/28	ELISA	Serum	NA
Boiko et al 2021	Russia	63	30	32/31	Multi-analyte panel	Serum	6 weeks

NA data non-available

Table 2 Description of the clinical features of the population selection

First author	Sorting tool	Schizophrenia patients (cases)	Healthy subjects (controls)
Zhang et al. 2009	DSM-III-R	Patients were chronically ill for a mean duration of 20.5 ± 10.2 years	Physical health based on complete physical, neurological, and psychiatric evaluations, and none had substance abuse or dependence except nicotine
Azizi et al. 2018	DSM-IV	Patients were diagnosed for the first time or relapsed due to a lack of compliance with therapy (assigned as the before treatment group)	No family history of mental disorder; no antidepressant, antipsychotic, or mood stabilizing drug use within the last 1 month
Erbagci et al. 2001	DSM-IV	None of them were alcohol consuming	Non-psychiatric controls recruited from the hospital staff
Borovcanin et al. 2013	ICD-10	Drug-naïve patients and in relapse	NA
Ding et al. 2014	DSM-IV	Disease duration less than 2 years and without antipsychotic treatment	Healthy controls were recruited from local communities and colleges through fliers
Kim et al. 2001	DSM-IV	Patients with acute psychotic state and no treatment with neuroleptic drugs for at least 6 months	NA
Noto et al. 2015	DSM-IV	Patients with no prior history of antipsychotic medication exposure	Controls and their first-degree family members had a negative lifetime history of major psychiatric disorder
Noto et al. 2015	DSM-IV	Antipsychotic-naïve patients	Individuals without a current or lifetime history of psychiatric disorders and with an absence of a major mental disorder in first-degree relatives were included
Noto et al. 2018	SCID-I	Antipsychotic-naïve patients	Individuals without a current or lifetime history of psychiatric disorders and with an absence of a major mental disorder in first-degree relatives were included
Song et al. 2013	DSM-IV	First-episode schizophrenia	Healthy control subjects with normal weight were recruited through advertisement
Lin et al. 2011	DSM-IV	All patients were in the acute stage, defined by the exacerbation of psychotic symptoms. All patients were drug free for at least 1 week prior to admission to our acute ward	Recruited from medical staff members and students with no past or familial history of any psychiatric disorder
Kim et al. 2009	DSM-IV	All patients had acute psychotic symptoms at the time of study enrollment and were either medication-naïve (first onset) or medication-free for at least 4 months	Healthy controls were recruited at the same hospital from among those who came for regular health screenings
Maes et al. 2000	DSM-IV	Exclusionary criteria for patients were other axis I diagnoses, such as organic mental disorder, substance use disorder, and affective disorders, as well as neurological	The healthy volunteers were free of any medication for at least 1 month prior to blood sampling
Pae et al. 2006	DSM-IV	Antipsychotic-naïve and antipsychotic-free more than 2 months	NA
Borovcanin et al. 2020	ICD-10	Schizophrenia in remission after a 3-month stable depot antipsychotic therapy	Healthy controls were recruited through the process of blood donation
Boiko et al 2021	ICD-10	The study did not include schizophrenia patients with acute and chronic infectious, inflammatory, and autoimmune diseases or patients who used psychoactive substances or took medications that could affect the metabolic or immunological parameters	NA

Table 3 Interleukin levels of schizophrenic patients with risperidone treatment and controls

First author	Interleukin levels		
	Pre-treatment (pg/ml)	Post-treatment (pg/ml)	Healthy controls (pg/ml)
IL-17A			
Borovcanin et al. 2020	1.99 ± 5.87		1.39 ± 2.71
Ding et al. 2014	17.69 ± 6.73	16.64 ± 6.80	15.61 ± 5.46
Noto et al. 2018	12.33 ± 0.92	9.29 ± 0.97	10.82 ± 10.9
Noto et al. 2015	2.31 ± 4.76	6.70 ± 15.11	4.26 ± 11.87
Borovcanin et al. 2013	6.57 ± 4.62	3.06 ± 3.06	30.86 ± 13.95
Borovcanin et al. 2013	62.59 ± 62.59	39.34 ± 39.34	30.86 ± 13.95
Boiko et al. 2021	4.61 (3.75; 5.55)	4.50 (3.87; 5.39)	
IL-10			
Noto et al. 2015	0.89 ± 2.52		0.20 ± 0.45
Noto et al. 2018	7.20 ± 0.23	6.02 ± 0.24	6.44 ± 0.27
Noto et al. 2015	0.84 ± 1.01	0.21 ± 0.34	0.20 ± 0.45
Pae et al. 2006	3.8 ± 1.0	4.9 ± 3.8	
Boiko et al. 2021	8.00 (7.08; 10.84)	8.00 (6.60; 1.01)	
IL-4			
Noto et al. 2018	13.75 ± 2.24	8.18 ± 2.35	13.36 ± 2.64
Noto et al. 2015	0.43 ± 0.78	0.03 ± 0.09	0.24 ± 0.63
Kim et al. 2009	46.91 ± 5.27	38.70 ± 3.48	268.72 ± 8.34
Borovcanin et al. 2013	25.1 ± 10.73	6.14 ± 2.31	12.09 ± 8.0
Borovcanin et al. 2013	7.19 ± 2.0	7.19 ± 2.0	12.09 ± 8.0
Boiko et al. 2021	81.48 (69.68; 96.15)	83.85 (69.70; 134.07)	
IL-2			
Zhang et al. 2009	9.8 ± 4.7	7.2 ± 4.9	3.3 ± 1.4
Kim et al. 2001	1.29 ± 3.92	0.70 ± 2.06	
Noto et al. 2018	2.34 ± 0.61	1.59 ± 0.64	2.43 ± 0.71
Kim et al. 2009	140.33 ± 24.20	206.95 ± 35.58	255.18 ± 17.57
Maes et al. 2000			
Pae et al. 2006	1.9 ± 3.3	2.0 ± 4.7	
Boiko et al. 2021	4.91 (4.38; 5.50)	5.19 (4.49; 5.80)	
IL-1B			
Azizi et al. 2019	35.39 ± 18.37	12.48 ± 6.96	11.96 ± 3.54
Erbagci et al. 2001	5.0 (5.0–11.6)		5.0 (5.0-5.0)
Kim et al. 2001	1.175 ± 0.75	0.95 ± 0.58	
Song et al. 2013	53.28 ± 12.62	53.64 ± 16.22	23.49 ± 15.27
Wang et al. 2016	1.62 ± 1.96	0.89 ± 0.63	0.81 ± 0.64
Boiko et al. 2021	2.49 (1.98; 3.23)	2.33 (1.83; 2.91)	
IL-8			
Erbagci et al. 2001	10.2 (5.0–1683.0)		8.5 (5.0–233.0)
Noto et al. 2018	9.78 ± 1.38	5.27 ± 1.45	9.78 ± 1.38
Wang et al. 2016	2.81 ± 3.91	2.20 ± 3.62	2.49 ± 2.21
Boiko et al. 2021	12.04 (8.77; 18.99)	13.03 (9.41; 17.36)	
IL-6			
Zhang et al. 2009	0.3 ± 0.5	0.2 ± 0.4	0.2 ± 0.2
Azizi et al. 2018	95.22 ± 70.52	39.22 ± 9.95	15.3 ± 5.69
Erbagci et al. 2001	5 ± 6.6		5 ± 3.8
Borovcanin et al. 2020	15.76 ±	38.58	13.56 ± 3.1
Ding et al. 2014	14.75 ± 4.52	13.94 ± 5.77	11.76 ± 5.05
Kim et al. 2001	4.39 ± 5.84	5.32 ± 6.34	
Noto et al. 2015	3.23± 15.27		0.77 ± 1.04

Table 3 (continued)

First author	Interleukin levels		
	Pre-treatment (pg/ml)	Post-treatment (pg/ml)	Healthy controls (pg/ml)
Noto et al. 2018	3.08 ± 0.29	1.46 ± 0.31	1.47 ± 0.34
Noto et al. 2015	1.64 ± 1.77	0.9 ± 0.81	0.77 ± 0.04
Song et al. 2013	33.98 ± 14.13	37.13 ± 13.23	15.53 ± 7.16
Lin et al. 2011	4.23 ± 6.28	3.17 ± 2.34	1.42 ± 1.72
Kim et al. 2009	487.56 ± 13.87	451.55 ± 15.95	234.08 ± 4.04
Maes et al. 2000	4 ± 6.24	7.2 ± 5.36	0.42 ± 0.42
Pae et al. 2006	25.7 ± 19.4	16.2 ± 10.1	
Borovcanin et al. 2013	27.85 ± 8.07	19.86 ± 6.16	8.14 ± 3.47
Borovcanin et al. 2013	16.25 ± 9.98	7.37 ± 4.39	8.14 ± 3.47
Boiko et al. 2021	6.67 (4.46; 9.55)	5.56 (3.99; 8.28)	

the groups of individuals with schizophrenia [23, 24]. With regard to IL-1B levels, a decrease in serum and plasma was reported in individuals with schizophrenia [7, 10, 27, 28]. Nevertheless, one study reported no differences in IL-1B levels after risperidone treatment in individuals with schizophrenia [8]. Finally, individuals with schizophrenia showed decreased levels of IL-8 after risperidone treatment [12, 27].

Cytokine Levels in Case-Control Studies

Studies that measured interleukin levels in individuals with psychiatric disorders were analyzed and their behavior was compared with healthy people. In some studies that evaluated IL-17A, lower levels of this interleukin were found in individuals with psychiatric diagnoses compared to control groups [20, 25]. Other studies, however, observed elevated levels of IL-17A in psychiatric individuals compared to control groups [11, 12, 29]. For IL-10, IL-1B, and IL-8 levels, studies showed high levels of interleukins in individuals with schizophrenic disorder [8–10, 12, 20]. Low levels of IL-2 were also observed compared to healthy people [12, 24]. Nonetheless, one study observed high levels of IL-2 compared to controls [26]. Studies that analyzed IL-4 levels observed elevated levels of this interleukin with little difference compared to controls [12, 20, 25]. One study, however, reported a marked increase of IL-4 levels compared to controls [24].

Discussion

One of the main characteristics of individuals with psychiatric disorders is a prolonged drug treatment [30, 31]. On the other hand, results of various studies show a possible association between baseline levels of certain interleukins and psychiatric illness such as schizophrenia [32–35]. In this regard, it has been observed that certain typical drugs can cause metabolic changes after a prolonged use [36, 37]. Therefore, effects of these drugs may be changing the concentration of pro-inflammatory and anti-inflammatory cytokines in individuals who are treated with those drugs; however, a conclusion has not been reached yet. Hence, our aim was to perform a systematic review in order to get a better perspective of the effects of risperidone on interleukin levels in individuals with schizophrenia.

The studies that evaluated the effects of risperidone in individuals with psychiatric disorders used plasma or serum; in the same way, various techniques and instruments were used to measure the levels of interleukins (ELISA, immunohistochemistry, flow cytometry). We observed that the main interleukins analyzed were IL-6, IL-17A, IL-10, IL-4, IL-2, IL-1B, and IL-8. Although there are a considerable number of interleukins analyzed and certain studies varied widely in their results, the majority of studies reported a correlation between risperidone treatment and decreased levels of interleukins [26, 27]. Nevertheless, in a study in an Iran population of 24 patients with schizophrenia and 24 healthy controls, there was no significant difference in IL-6, IL-1β, and IL-2 levels between patients before/after treatment and healthy subjects [10]. It is possible the different findings were due to the type of sample and the detection technique used. A possible solution is to perform more studies with homogeneous methodologies in order to compare the results more accurately. For example, there are some challenge when measuring cytokine biomarkers such as interleukins, from pre-analytical factors (e.g., age, gender, hormones) to technical methods, (e.g., sample handling, choice of medium, storage), for example, an evidence, which reports that some cytokines (e.g., IL-6) were more stable in plasma than in whole blood after sampling [38]. In fact, some researchers suggest that plasma and serum are not exchangeable in measurement cytokines [39]. In this sense, serum sample is lacking fibrinogen, platelets, and other coagulation factors and during the clotting process,

cytokines are released. Therefore, these are some explanations in the differences on the measures of interleukin levels [40]. On the other hand, the effect on cytokine stability of storage duration prior to sample freezing should be considered. Concerning that, a study reports a significant signal degradation from the fourth day of storage in a single analyte [41]. Consequently, these and others factors implicated in the stability of the interleukins should be taken in consideration.

In addition to the association between the treatment with risperidone and the levels of interleukins in the bloodstream, it is important to remember that interleukins may have an implication in the development of psychiatric illnesses. Bearing this in mind, it is important to evaluate the behavior of these interleukins without the intervention of drugs such as risperidone in order to understand the concentration changes of these interleukins before receiving any drug treatment. Another perspective on the role of risperidone on interleukin levels is to compare with groups of healthy people in order to detect if the disease is itself a factor that influences interleukin levels.

It is important to mention the findings of the studies that evaluated the levels of interleukins in individuals with schizophrenia compared to controls. Taking this into account, the results showed significantly higher levels of certain interleukins (IL-2, IL-6, IL-1B, IL-12, IL-10, IL-4, IL-8) in cases compared to controls. However, a study that found no differences in cases before and after treatment also observed no differences when compared to the control group [42]. This type of results gives us the guideline to evaluate other factors that may intervene in the levels of these interleukins regardless of the treatment and the disease, such as age, sex, ethnicity, external treatments, and the environment itself. For this reason, studies that evaluate as many factors as possible are necessary in order to obtain consistent results.

The pharmacological treatment with risperidone has been observed to alter interleukin levels in other diseases; some studies have shown that risperidone changes the levels of IL-8 and IL-1β, as well as the levels of BNDF and TGF-β1 expression [27]. Another example of the importance of evaluating the effect of risperidone on interleukin levels is that of Obuchowicz et al., who evaluated the effect of risperidone on mixed glial cells of rats induced with lipopolysaccharides, finding that under a strong inflammatory activation, risperidone decreased the levels of TNF-α and IL-1β [43]. Examples like these show the importance of evaluating the various factors that could alter interleukin levels.

Risperidone is a second-generation atypical antipsychotic drug that is widely used for the treatment of psychiatric illnesses such as mania or schizophrenia [44, 45]. Medical treatment with this drug has been associated with alterations of certain interleukin levels, liver damage, and development of metabolic syndrome [1, 46].

The cytokine hypothesis of schizophrenia could start because interleukins influence neurodegenerative and neuroprotective processes in the brain. Furthermore, they are involved in the modulation of synaptic plasticity. Therefore, an imbalance in interleukin levels represents vulnerability to immune inflammatory process and subsequently can cause an impairment of brain functions [47]. The most common explanation studied is the microglial activation, which triggers interleukin productions. For example, in patients with schizophrenia, a marked number of microglia in temporal and frontal cortex have been detected; which may reflect a dysfunction [48].

To date, there is no definite explanation of how these changes in interleukin levels occur after drug treatment, whether they decrease or increase. One possible explanation for the increase of interleukin levels is the appearance of hyperphagia after treatment with risperidone due to the reduction of the 5HT2C receptor activity, which increases food intake [49, 50]. On the other hand, a reduction in activity and energy expenditure has been observed in individuals treated with this drug, which is caused by the blockade of dopamine receptors, causing weight gain [51]. Although risperidone is a drug characterized by reducing the characteristic side effects of its past generation, studies show that treatment with these antipsychotic drugs can cause metabolic alterations including obesity, hypertension, and diabetes among others [3, 52].

On the other hand, the majority of studies reported a decrease in interleukin levels after risperidone treatment. A possible explanation is due to astrocyte activity; some studies have found that risperidone has an anti-inflammatory effect on astroglia C6, which reduces IL-6 levels [53]. Other study concluded that risperidone decreased the secretion of S100B induced by IL-6 [54]. Another explanation is related to the production of IL-6 that occurs in neurons, astrocytes, and microglia [55]. With this in mind, one study showed that risperidone can decrease the activation of microglia in the brain, which could lower IL-6 levels [56]. There are complications that can be developed due to the decrease of interleukin concentrations; the decrease of IL-5, for example, is related to the inhibition of the differentiation of oxidized characteristic low-density lipoproteins and the decrease of Th1 and Th17 and their interleukins [57]. A detailed proposal is shown in Fig. 3. We also observed that individuals with schizophrenia had higher levels of certain interleukins compared to the healthy population; therefore, it is necessary to take into account the basal levels of those interleukins that are affected by psychiatric illnesses before evaluating them after receiving antipsychotic drug treatments, in order to determine more accurately the possible side effects that drugs may cause. It is important to study the effect of risperidone as an antipsychotic drug and their side effects, all in

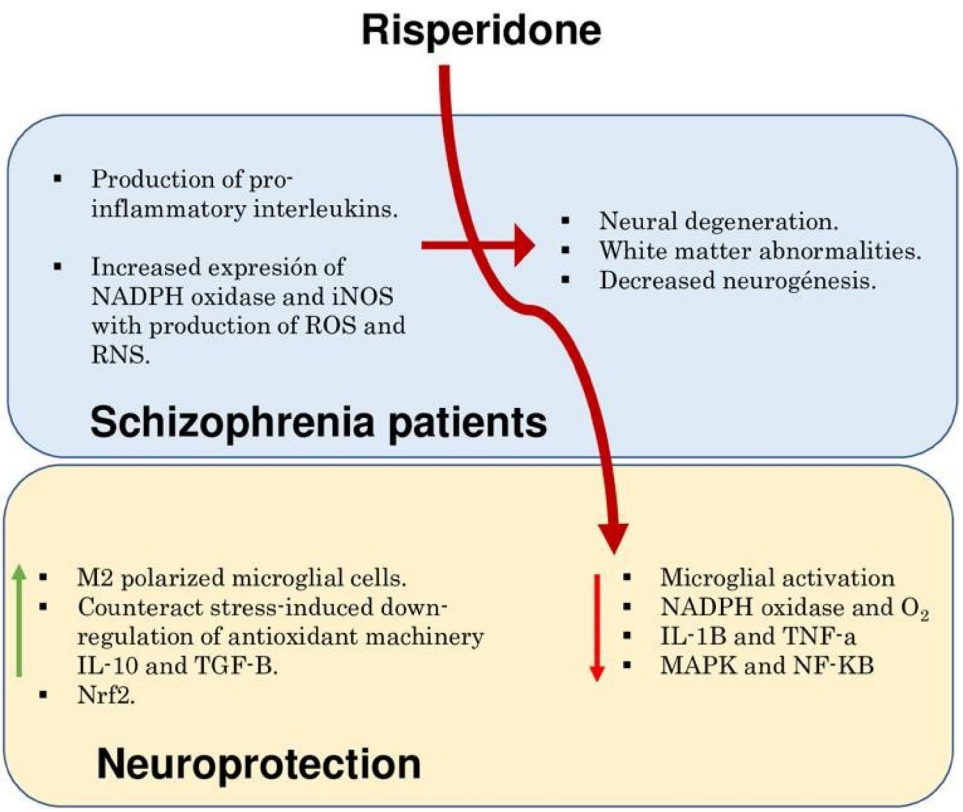

Fig. 3 Possible neuroprotective effect of risperidone on microglia in schizophrenia: therapeutic antipsychotic potential

order to generate a specialized pharmacological treatment with the fewest possible complications.

It is necessary to recognize some limitations in this study: the first is that the sample size can be considered small. The variety of samples and techniques used, along with the small number of studies, did not allow a more homogeneous analysis due to the established inclusion criteria. The inclusion of more studies is necessary to increase the robustness of our findings. Another limitation is that factors such as age, sex, and geographical area were not evaluated, since these may be related to the effects of risperidone on cytokine levels. Finally, we did not include articles that evaluated samples other than plasma or serum; this could be considered a limitation, particularly because we did not evaluate interleukins obtained from central samples. However, we believe that our results may broaden the picture of the effects of antipsychotic drugs in individuals with schizophrenia for future reference on treatments and side effects.

Conclusions

We observed that the levels of certain interleukins were altered due to the prolonged use of antipsychotic drugs such as risperidone. As these interleukins can be affected by uncontrolled factors within the population, it is necessary to perform more studies that thoroughly address other factors that may intervene in the levels of interleukins, as well as using larger and more homogeneous samples.

Author Contribution MARM, CATZ, IEJR, MLLN, and TBGC designed the study and wrote the protocol; MARM, CATZ, IEJR, MLLN, ADGM, TBGC, JJMM, GEVJ, MBR, and RGCA managed the literature searches and analyses; YHD, CATZ, ADGM, TBGC, and JJMM undertook the statistical analysis, and MARM, CATZ, IEJR, MLLN, TBGC, GEVJ, MBR, RGCA, and RFOO wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Data Availability Not applicable for this manuscript.

Code Availability Not applicable.

Declarations

Ethics Approval None applicable.

Consent for Publication All authors consent to the publication of the present work.

Conflict of Interest The authors declare no conflict of interest.

References

1. McNeil SE, Gibbons JR, Cogburn M. Risperidone. In StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan 16 PMID: 29083663.
2. Arango C, et al. Lurasidone compared to other atypical antipsychotic monotherapies for adolescent schizophrenia: a systematic literature review and network meta-analysis. Eur Child Adolesc Psychiatry. 2020;29(9):1195–205.
3. Shenoi SD, et al. Update on pharmacotherapy in psychodermatological disorders. Indian Dermatol Online J. 2020;11(3):307–18.
4. Yunusa I, El Helou ML. The use of risperidone in behavioral and psychological symptoms of dementia: a review of pharmacology, clinical evidence, regulatory approvals, and off-label use. Front Pharmacol. 2020;11:596.
5. Barton BB, et al. Prevalence of obesity, metabolic syndrome, diabetes and risk of cardiovascular disease in a psychiatric inpatient sample: results of the Metabolism in Psychiatry (MiP) Study. Eur Arch Psychiatry Clin Neurosci. 2020;270(5):597–609.
6. Tsai HP, et al. Risperidone exacerbates glucose intolerance, nonalcoholic fatty liver disease, and renal impairment in obese mice. Int J Mol Sci. 2021;22(1)
7. Kim D-J, et al. Effect of risperidone on serum cytokines. Int J Neurosci. 2001;111(1-2):11–9.
8. Song X, et al. Changes in pro-inflammatory cytokines and body weight during 6-month risperidone treatment in drug naïve, first-episode schizophrenia. Psychopharmacology (Berl). 2014;231(2):319–25.
9. Noto C, et al. Depression, cytokine, and cytokine by treatment interactions modulate gene expression in antipsychotic naïve first episode psychosis. Mol Neurobiol. 2016;53(8):5701–9.
10. Azizi E, et al. Alteration of serum levels of cytokines in schizophrenic patients before and after treatment with risperidone. Iran J Allergy Asthma Immunol. 2019;18(3):262–8.
11. Ding M, et al. Activation of Th17 cells in drug naïve, first episode schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2014;51:78–82.
12. Noto MN, et al. Activation of the immune-inflammatory response system and the compensatory immune-regulatory system in antipsychotic naive first episode psychosis. Eur Neuropsychopharmacol. 2019;29(3):416–31.
13. Solmi M, et al. Safety of 80 antidepressants, antipsychotics, anti-attention-deficit/hyperactivity medications and mood stabilizers in children and adolescents with psychiatric disorders: a large scale systematic meta-review of 78 adverse effects. World Psychiatry. 2020;19(2):214–32.
14. da Silva Araújo T, et al. Reversal of schizophrenia-like symptoms and immune alterations in mice by immunomodulatory drugs. J Psychiatr Res. 2017;84:49–58.
15. Bishop JR, Pavuluri MN. Review of risperidone for the treatment of pediatric and adolescent bipolar disorder and schizophrenia. Neuropsychiatr Dis Treat. 2008;4(1):55–68.
16. Gupta S, Black DW, Smith DA. Risperidone: review of its pharmacology and therapeutic use in schizophrenia. Ann Clin Psychiatry. 1994;6(3):173–80.
17. Sárvári AK, et al. Atypical antipsychotics induce both proinflammatory and adipogenic gene expression in human adipocytes in vitro. Biochem Biophys Res Commun. 2014;450(4):1383–9.
18. Al-Amin MM, Nasir Uddin MM, Mahmud Reza H. Effects of antipsychotics on the inflammatory response system of patients with schizophrenia in peripheral blood mononuclear cell cultures. Clin Psychopharmacol Neurosci. 2013;11(3):144–51.
19. MacDowell KS, et al. Risperidone normalizes increased inflammatory parameters and restores anti-inflammatory pathways in a model of neuroinflammation. Int J Neuropsychopharmacol. 2013;16(1):121–35.
20. Noto C, et al. Effects of risperidone on cytokine profile in drug-naïve first-episode psychosis. Int J Neuropsychopharmacol. 2014;18(4)
21. Tourjman V, et al. Antipsychotics' effects on blood levels of cytokines in schizophrenia: a meta-analysis. Schizophr Res. 2013;151(1-3):43–7.
22. Frydecka D, et al. Profiling inflammatory signatures of schizophrenia: a cross-sectional and meta-analysis study. Brain Behav Immun. 2018;71:28–36.
23. Pae CU, et al. Antipsychotic treatment may alter T-helper (TH) 2 arm cytokines. Int Immunopharmacol. 2006;6(4):666–71.
24. Kim YK, et al. Cytokine changes and tryptophan metabolites in medication-naïve and medication-free schizophrenic patients. Neuropsychobiology. 2009;59(2):123–9.
25. Borovcanin M, et al. Antipsychotics can modulate the cytokine profile in schizophrenia: attenuation of the type-2 inflammatory response. Schizophr Res. 2013;147(1):103–9.
26. Zhang XY, et al. Superoxide dismutase and cytokines in chronic patients with schizophrenia: association with psychopathology and response to antipsychotics. Psychopharmacology (Berl). 2009;204(1):177–84.
27. Wang TY, et al. Comparing clinical responses and the biomarkers of BDNF and cytokines between subthreshold bipolar disorder and bipolar II disorder. Sci Rep. 2016;6:27431.
28. Boiko AS, et al. Cytokine level changes in schizophrenia patients with and without metabolic syndrome treated with atypical antipsychotics. Pharmaceuticals (Basel). 2021;14(5)
29. Borovcanin MM, et al. Type 17 immune response facilitates progression of inflammation and correlates with cognition in stable schizophrenia. Diagnostics (Basel). 2020;10(11)
30. Millan MJ, et al. Learning from the past and looking to the future: emerging perspectives for improving the treatment of psychiatric disorders. Eur Neuropsychopharmacol. 2015;25(5):599–656.
31. Correll CU. Pharmacotherapy of schizophrenia. Nervenarzt. 2020;91(1):34–42.
32. Na KS, Jung HY, Kim YK. The role of pro-inflammatory cytokines in the neuroinflammation and neurogenesis of schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2014;48:277–86.
33. Ramírez-Jirano LJ, et al. Cytokines and nervous system: relationship with schizophrenia. Rev Med Inst Mex Seguro Soc. 2019;57(2):107–12.
34. Mohammadi A, Rashidi E, Amooeian VG. Brain, blood, cerebrospinal fluid, and serum biomarkers in schizophrenia. Psychiatry Res. 2018;265:25–38.
35. Borovcanin MM, et al. Interleukin-6 in schizophrenia-is there a therapeutic relevance? Front Psychiatry. 2017;8:221.
36. Ijaz S, et al. Antipsychotic polypharmacy and metabolic syndrome in schizophrenia: a review of systematic reviews. BMC Psychiatry. 2018;18(1):275.
37. Zhang JP, et al. Pharmacogenetic associations of antipsychotic drug-related weight gain: a systematic review and meta-analysis. Schizophr Bull. 2016;42(6):1418–37.
38. Hennø LT, et al. Effect of the anticoagulant, storage time and temperature of blood samples on the concentrations of 27 multiplex assayed cytokines - Consequences for defining reference values in healthy humans. Cytokine. 2017;97:86–95.
39. Krishnan VV, et al. Multiplexed measurements of immunomodulator levels in peripheral blood of healthy subjects: effects of analytical variables based on anticoagulants, age, and gender. Cytometry B Clin Cytom. 2014;86(6):426–35.
40. Brøndum L, et al. An evaluation of multiplex bead-based analysis of cytokines and soluble proteins in archived lithium heparin

plasma, EDTA plasma and serum samples. Scand J Clin Lab Invest. 2016;76(8):601–11.
41. Vincent FB, et al. Effect of storage duration on cytokine stability in human serum and plasma. Cytokine. 2019;113:453–7.
42. Erbağci AB, et al. Serum IL-1beta, sIL-2R, IL-6, IL-8 and TNF-alpha in schizophrenic patients, relation with symptomatology and responsiveness to risperidone treatment. Mediators Inflamm. 2001;10(3):109–15.
43. Obuchowicz E, et al. Different influence of antipsychotics on the balance between pro- and anti-inflammatory cytokines depends on glia activation: an in vitro study. Cytokine. 2017;94:37–44.
44. Risperidone, in LiverTox: Clinical and research information on drug-induced liver injury. 2012 Feb 16, National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda (MD) Publishing [Internet]. PMID: 31643176
45. Chopko TC, Lindsley CW. Classics in chemical neuroscience: risperidone. ACS Chem Neurosci. 2018;9(7):1520–9.
46. Hirsch L, et al. Second-generation antipsychotics and metabolic side effects: a systematic review of population-based studies. Drug Saf. 2017;40(9):771–81.
47. Watanabe Y, Someya T, Nawa H. Cytokine hypothesis of schizophrenia pathogenesis: evidence from human studies and animal models. Psychiatry Clin Neurosci. 2010;64(3):217–30.
48. Leonard BE. Is there an immunologic basis for schizophrenia? Expert Rev Clin Immunol. 2005;1(1):103–12.
49. Sum-Ping O, Guilleminault C. Kleine-Levin syndrome. Curr Treat Options Neurol. 2016;18(6):24.
50. Wan XQ, et al. Risperidone stimulates food intake and induces body weight gain via the hypothalamic arcuate nucleus 5-HT2c receptor-NPY pathway. CNS Neurosci Ther. 2020;26(5):558–66.
51. Beeler JA, et al. Low dopamine D2 receptor increases vulnerability to obesity via reduced physical activity, not increased appetitive motivation. Biol Psychiatry. 2016;79(11):887–97.
52. Bretler T, et al. The effects of antipsychotic medications on microbiome and weight gain in children and adolescents. BMC Med. 2019;17(1):112.
53. Bobermin LD, et al. Differential effects of typical and atypical antipsychotics on astroglial cells in vitro. Int J Dev Neurosci. 2018;69:1–9.
54. Robinson-Agramonte MLA, Pedre LL, Serrano-Barrera OR. Neuroimmunology research. a report from the Cuban network of neuroimmunology. Behav Sci (Basel). 2018;8(5)
55. Nurjono M, Lee J, Chong SA. A review of brain-derived neurotrophic factor as a candidate biomarker in schizophrenia. Clin Psychopharmacol Neurosci. 2012;10(2):61–70.
56. Al-Amin MM, et al. Pretreatment with risperidone ameliorates systemic LPS-induced oxidative stress in the cortex and hippocampus. Front Neurosci. 2018;12:384.
57. Ye D, et al. Interleukin-5 levels are decreased in the plasma of coronary artery disease patients and inhibit Th1 and Th17 differentiation in vitro. Rev Esp Cardiol (Engl Ed). 2020;73(5):393–402.