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Iron homeostasis alterations and risk for akathisia in patients treated with antipsychotics: a systematic review and meta-analysis of cross-sectional studies

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Abstract

Iron homeostasis may be implicated in the pathophysiology of antipsychotic-related akathisia. We performed a systematic review in six databases from database inception until 03/2020, conducting a meta-analysis of studies investigating iron metabolism in antipsychotic-treated patients with versus without akathisia. Using a fixed- and a random-effects model, standardized mean difference (SMD) was estimated for levels of iron, ferritin, transferrin and total iron-binding capacity. Meta-regression analyses included sex, age, illness duration and antipsychotic treatment and dose. Subgroup analyses included chronic vs. acute akathisia and different diagnoses. Study quality was assessed using the Newcastle-Ottawa scale. In 10 studies (n=395), compared to non-akathisia patients (n=213), iron levels were lower in patients with akathisia (n=182; fixed-effect model: SMD=-0.49, 95%CI=-0.28,-0.70, p<0.001; random-effects model: SMD=-0.55, 95%CI=-0.14,-0.96, p=0.008). For secondary outcomes, differences were significant regarding lower ferritin levels in patients with akathisia in the fixed-effect model (SMD=-0.32, 95%CI=-0.08,-0.55, p=0.007), but not in the random-effects model (SMD=-0.29, 95%CI=0.20,-0.79, p=0.24). None of the moderators/mediators had a significant effect on the group difference of iron levels. Subgroup analyses reported lower iron levels in both patients with chronic and acute akathisia vs. patients without. Iron levels for schizophrenia patients were lower in the fixed-effect model (SMD=-0.55, 95%CI=-0.23, -0.86, p<0.001), while a trend was observed in the random-effects model (SMD=-0.52, 95%CI=-0.07, -1.12, p=0.08). The studies' quality was overall poor, with one exception. This meta-analysis suggests lower iron levels in akathisia patients, while ferritin differences were significant only in the fixed-effect model. Further data are required to promote the understanding of related pathways.

Keywords: iron metabolism; iron; akathisia; antipsychotic; movement disorders; meta-analysis

1. Introduction

Iron is a fundamental trace element implicated in numerous vital processes of human physiology (Andrews, 1999). Involvement of iron homeostasis disturbances has been hypothesized in the context of the pathophysiology for different mental illnesses (Kim et al., 2018; Percinel et al., 2016; Quinn et al., 2011; Shorter and Wachtel, 2013). In the context of schizophrenia, iron excess may be related to toxicity underpinning cognitive deficits (Cao et al., 2019). In particular, iron deficiency has also received attention in light of the mechanisms underlying motor symptoms associated with antipsychotic treatment. For example, lower iron levels were reported in patients with versus without catatonic symptoms (Peralta et al., 1999), whereas no differences were reported in patients developing antipsychotic-related dystonic reactions or tardive dyskinesia (Chong et al., 2004; Sachdev, 1994; Spina et al., 1994).

Iron homeostasis status markers have been more extensively studied in patients with akathisia, which is a relatively common adverse effect of both first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs). In an overview of meta-analyses and Cochrane reviews, prevalences of akathisia ranged from 15.9% with chlorpromazine and 24.1% for haloperidol for FGAs, and from 3.3% with paliperidone and 5.2% with quetiapine to 8.5% with aripiprazole, 11.3% with amisulpride and 14.2% with risperidone for SGAs (Martino et al., 2018). In a meta-analysis of 48 studies of the most recently approved SGAs, the weighted mean incidence of akathisia was 7.7% (95% confidence interval (CI)=6.5-9.1), ranging from 3.9% (95%CI=2.4-6.3) for iloperidone to 6.8% (95%CI=5.1-9.0) for asenapine, 10.0% (95%CI=7.4-13.5) for brexpiprazole, 12.7% (95%CI=10.1-16.1) for lurasidone, and 17.2% (95%CI-13.4-22.1) for cariprazine (Demyttenaere et al., 2019). Several cross-sectional studies reported lower iron levels in patients with versus without antipsychotic-related akathisia (Barton et al., 1990; Brown et al., 1987; Hofmann et al., 2000; Horiguchi, 1991; Kuloglu et al., 2003; Valles et al., 1992), while other studies did not detect significant differences (Barnes et al., 1992; Juncal-Ruiz et al., 2017; Nemes et al., 1991; O'Loughlin et al., 1991; Soni et al., 1993). Discrepancies in these findings may be at least partially due to different demographic and clinical characteristics of study samples (Friedman, 1991). Further, two of these studies also included individuals without psychiatric diagnoses/medication as an additional control group (Kuloglu et al., 2003; Nemes et al., 1991). In one sample, a ranking order with iron levels being higher in healthy controls followed by patients without and finally those with akathisia was observed (Kuloglu et al., 2003), whereas in another sample, no significant intergroup differences were reported (Nemes et al., 1991).

There are two major frameworks linking depletion of iron stores and antipsychotic-related akathisia. One hypothesis explains this association in terms of direct antipsychotic-related effects on iron status (Calarge and Ziegler, 2013; O'Loughlin et al., 1991). Preclinical and clinical evidence have provided hints on psychotropic medications, including antipsychotics, such as aripiprazole and mixed SGAs, affecting levels of factors involved in maintaining iron homeostasis (Bogdan et al., 2015; Chen et al., 2018). For example, in aripiprazole-treated rats, elevated glycoprotein levels were reported, which is implicated in hepcidin response to iron depletion (Bogdan et al., 2015). Moreover, a case-control study assessed trace elements before and after treatment with SGAs in newly diagnosed patients with schizophrenia reporting lower iron levels at baseline compared to healthy controls (Chen et al., 2018). Antipsychotic treatment effects were only reported in males with elevated follow-up iron levels, whereas duration of antipsychotic treatment did not affect iron levels (Chen et al., 2018). Another possibility is that patients with low iron levels are at high-risk of developing akathisia, with pathways still remaining to be elucidated (Sachdev and Loneragan,

1991). A proposed link may encompass the oxidative effects of iron depletion on the dopaminergic system in the basal ganglia (Yanik et al., 2004), in that antipsychotic-related dopamine receptor upregulation leads to decreased inhibitory activity as well as dopamine receptor hypersensitivity (Solmi et al., 2018a; Solmi et al., 2018b). Nevertheless, prospective short-term data have not supported this hypothesis (O'Loughlin et al., 1991; Sachdev and Loneragan, 1991). However, medium-term or long-term antipsychotic-related effects on iron status are poorly understood. As early interest wore off, this area has not received attention in recent years. Conversely, the awareness of the need to identify and treat movement abnormalities in people with schizophrenia and movement disorders associated with antipsychotics has increased (Carbon et al., 2018; Demyttenaere et al., 2019; Martino et al., 2018; Solmi et al., 2018a; Solmi et al., 2018b). Thus, the purpose of this study was to systematically review and meta-analyse data on blood measures of iron status in adults with versus without antipsychotic-associated akathisia.

2. Experimental procedures

2.1. Search strategy

The study was conducted with use of PRISMA guidelines (Hutton et al., 2015) and registered with PROSPERO (registration number CRD42019121376). Studies of iron status and akathisia were identified by searching Embase and Medline using the following strategy: “iron” AND “akathisia”. Databases were searched last in January 15, 2019 for publications without language restriction since data inception. References from identified studies were hand-searched for additional studies. An additional search in Scopus, PsycInfo, Googlescholar and Cochrane Library was performed on March 15, 2020.

2.2. Inclusion & exclusion criteria

Type of studies

Included were observational studies in antipsychotic-treated adults reporting on blood concentrations of iron status markers in patients with versus without antipsychotic-related akathisia regardless of the diagnosis and the setting. Case reports were not included.

Types of participants

Antipsychotic-treated adult patients of both sexes with versus without antipsychotic-related akathisia. There were no restrictions with regards to psychiatric diagnosis, setting, and dosage or duration of antipsychotic treatment. Patients receiving antipsychotic monotherapy as well as polypharmacy were considered. Patients with neurological diseases were excluded.

Comparator

Patients exposed to antipsychotics without antipsychotic-related akathisia.

Types of exposure

Any type of akathisia regardless of the assessment method in patients treated with antipsychotics.

Outcomes

The primary outcome was defined as standardized mean difference (SMD) for iron blood concentrations between patients with versus without antipsychotic-related akathisia. Secondary outcomes included SMDs for ferritin, transferrin and TIBC.

Selection of eligible studies was independently performed by two authors (GS and DG). In case of doubt, papers were discussed and consensus was reached. As consensus was reached in all cases, no additional co-author was involved.

2.3. Data extraction

One author (GS) extracted data, which were independently verified by another author (DG). Sample sizes, demographic characteristics, akathisia ratings, daily antipsychotic dosages, iron, ferritin, transferrin concentration as well as total iron-binding capacity (TIBC) values (mean and standard deviation [SD]) were extracted. Before data entry, values were converted to the same unit for each parameter. Weighted means for covariates were computed based on means of subgroups. One study provided levels for a group with tardive akathisia and dyskinesia (Sachdev, 1994). Based on provided data, means were computed for patients exclusively suffering from akathisia symptoms, while SDs of the whole group were adopted. The same strategy for missing SDs was applied in another study, where SDs for the whole group were available (O'Loughlin et al., 1991). In three studies (Barton et al., 1990; Brown et al., 1987; Horiguchi, 1991), data for means and variance measures were extracted from figures using the WebPlotDigitlizer (version 4.2 for Windows); in one of the studies, authors provided a mean value for four blood samples withdrawn within two days (Barton et al., 1990). In two cases, authors were contacted to provide missing data (Barnes et al., 1992; Treloar et al., 1994), but no data were available, given the age of the studies.

2.4. Quality of studies

The Newcastle-Ottawa scale for case-control studies and the modified version for cross-sectional studies were used for quality assessment (Herzog et al., 2013; Wijarnpreecha et al., 2019). For cross-sectional studies, we removed the item “representativeness of the exposed cohort” that we judge related to applicability, and added ascertainment of akathisia as described elsewhere (Li et al., 2016).

2.5. Statistical analysis

Outcomes were compared between groups of patients with versus without akathisia using fixed- and random-effects inverse-variance meta-analyses. Results were summarized using SMD and 95% confidence intervals (CI) and were presented in forest plots. Heterogeneity variance parameter (τ^2) was calculated using the DerSimonian-Laird estimator (DerSimonian and Laird, 1986). We also calculated the I-square (I^2) statistic, which measures the proportion of variability that can be attributed to heterogeneity rather than random error, with an I^2 >50% representing significant heterogeneity (Higgins et al., 2003). Thereafter, the effects of demographic and clinical parameters, including sex, age, duration of illness as well as antipsychotic treatment and daily dose (in chlorpromazine equivalents; CPZE) were assessed in a meta-regression analysis (Borenstein et al., 2009). We also included two subgroup analyses for the primary outcome, focusing separately on studies of patients i) with chronic or acute akathisia vs. controls, and ii) patients with schizophrenia-spectrum vs. affective disorders. All analyses were performed using the `meta` package in R for the analyses (Schwarzer et al., 2015).

2.6. Quality of meta-analytical evidence

We rated the quality of evidence according to the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group system (Balshem et al., 2011; Guyatt et al., 2008). GRADE allows rating the certainty of estimate for every outcome. We used the GRADEProGDT app for the summary of Findings tables. The following factors were considered: study design, risk of bias, consistency, precision, directness, presence of large, effect, dose–response gradient and publication bias.

3. Results

3.1. Search Results

The electronic data base search yielded 50 articles from Medline, 99 from Embase and two from the full-text reviewed articles' reference lists (Juncal-Ruiz et al., 2017; Spina et al., 1994). The additional search in Scopus, PsycInfo, Googlescholar and Cochrane Library did not yield any further articles of interest. After removing duplicates 128 articles remained. After exclusion of 103 articles based on title and abstract review, 25 articles were full-text screened, leading to rejection of 15 papers due to lack of iron levels (n=8), investigation of antipsychotic-related movement disorders other than akathisia (n=3), failure to provide/extract data for mean iron levels per study group (n=2), iron supplementation studies (n=1), and case reports (n=1). Ultimately, 10 studies fulfilled all inclusion criteria and were used for data extraction (Supplementary Figure 1).

3.2. Study and patient characteristics

We meta-analyzed 10 cross-sectional studies with 395 patients (mean age=42.2±9.1 years, 34.5% females, 85.6% schizophrenia-spectrum disorders, mean illness duration=18.3±6.3 years), of which 182 patients had akathisia) and 213 did not have akathisia (Table 1). Akathisia was assessed with a rating scale in nine (90%) of the ten studies. The mean duration of antipsychotic treatment was 12.9±5.54 years and the mean daily chlorpromazine equivalent dose was 875.05±271.6 mg/day. Seven (70.0%) of the ten studies adjusted the group comparison for demographic and antipsychotic dose differences (Table 1).

3.3. Primary outcome

In 10 studies (n=395) including 182 patients with and 213 patients without akathisia, iron blood levels were significantly lower in patients with versus without akathisia (fixed-effect model: SMD=-0.49, 95%CI=-0.28, -0.70, p<0.001; random-effects model: SMD=-0.55, 95%CI=-0.14, -0.96, p=0.008) (Figure 1). Heterogeneity was large (I^2=72%, τ^2=0.30). Differences did not essentially change after removing the three studies (Horiguchi, 1991; Nemes et al., 1991; O'Loughlin et al., 1991) that did not control for demographic and antipsychotic dose differences between study groups (fixed-effect model: SMD=-0.52, 95%CI=-0.27, -0.76, p<0.001; random-effects model: SMD=-0.51, 95%CI=-0.08, -0.95, p=0.02), while the heterogeneity decreased slightly, but remained substantial (I^2=67.5%, τ^2=0.23).

Figure 1 here

3.4. Secondary outcomes

Regarding ferritin levels (studies=7, n=310), the fixed-effect model yielded lower levels in patients with versus without akathisia (SMD=-0.32, 95%CI=-0.08, -0.55, p=0.007), whereas effects were not significant in the random-effects model (SMD=-0.29, 95%CI=-0.79, 0.20, p=0.24). Heterogeneity was substantial (I^2=77.6%, τ^2=0.35) (Figure 2).

For transferrin (studies=3, n=134), no significant differences were detected between groups using the fixed-effect model (SMD=0.08, 95%CI=-0.29, 0.45, p=0.67) or the random-effects model (SMD=-0.10, 95%CI=0.67, -0.88, p=0.79). Heterogeneity was large (I^2=75%, τ^2=0.35) (Figure 3).

Lastly, for TIBC (studies=6, n=238), no significant differences between patients with versus without akathisia were observed using the fixed-effect model (SMD=0.15, 95%CI=-0.11, 0.41, p=0.26) or the random-effects model (SMD=0.12, 95%CI=-0.29, 0.54, p=0.56) (Figure 4). Heterogeneity was substantial (I^2=60%, τ^2=0.16).

“Figures 2,3,4 here

3.5. Meta-regression analysis of iron level differences

The meta-regression for iron concentration differences demonstrated no significant influence for sex (estimated coefficient=-1.73, 95%CI=-4.00, 0.55, =-4.00 p=0.14), age (estimated coefficient=0.03, 95%CI=-0.03, 0.09, p=0.35), CPZE daily dosage (estimated coefficient=0.001, 95%CI=-0.001, 0.004, p=0.36), antipsychotic treatment duration (estimated coefficient=0.12, 95%CI=-0.05, 0.3, p=0.17) and illness duration in years (estimated coefficient=0.03, 95%CI=-0.07, 0.12, p=0.57).

3.6. Subgroup analyses

3.6.1. Iron differences in patients with chronic or acute akathisia vs. control group

In 7 studies (n=265), iron levels were significantly lower in patients with vs. without chronic akathisia (fixed-effect model: SMD=-0.56, 95%CI=-0.3, -0.81, p<0.001; random-effects model: SMD=-0.66, 95%CI=-0.08, -1.24, p=0.02). Heterogeneity was high (I^2=79.6%, τ^2=0.47). The same pattern was observed for patients with vs. without acute akathisia (SMD=-0.53, 95%CI=-0.07, -1.0, p=0.02 for both fixed- and random-effects modes in two studies with 86 patients). Heterogeneity was very low (I^2=0.0%, τ^2=0.0).

3.6.2. Iron differences in patients with schizophrenia-spectrum disorders

Four studies (n=176) assessed exclusively patients with schizophrenia-spectrum disorders: iron levels were lower in schizophrenia patients with vs. without chronic akathisia (fixed-effect model: SMD=-0.55, 95%CI=-0.23, -0.86, p<0.001), while a trend was observed in the random-effects model (SMD=-0.52, 95%CI=-0.07, -1.12, p=0.08). The heterogeneity was substantial (I^2=72.0%, τ^2=0.26). As the rest of study samples had mixed diagnoses and data were provided in aggregate form, we were unable to perform subgroup analyses for any other diagnoses.

3.7. Quality assessment

The assessment of risk of bias was invariably hampered by the scarcity of provided information. Lack of critical information included assessment methods for akathisia as well as iron levels, blinding of akathisia

raters regarding the iron markers' levels, use of parametric tests without assessing normality of iron homeostasis data distributions, and comorbidities that may relate to iron alterations, such as restless leg syndrome (Matthews, 1976). Of studies included for the primary outcome, one was rated as high quality and the rest as poor quality (Supplementary Table S1).

3.8. GRADE assessment

For the primary and the secondary outcomes the certainty of the results was rated as very low; this was mainly due to inconsistency between studies as well as the baseline assumption of low certainty for observational studies (Supplementary Table S2).

4. Discussion

Although akathisia is a relatively common antipsychotic-related adverse event (Demyttenaere et al., 2019; Martino et al., 2018), the pathogenesis of akathisia and other antipsychotic-associated movement disorders remains poorly understood. In that context, early data have provided some insight on potential links between peripheral markers of iron homeostasis and akathisia (Barton et al., 1990; Brown et al., 1987; O'Loughlin et al., 1991). This meta-analysis provides preliminary evidence that lower iron blood levels were associated with antipsychotic-related akathisia in comparison to patients without akathisia. Based on animal models (Ashkenazi et al., 1982), it has been hypothesized that iron levels are linked to akathisia symptoms via central dopaminergic transmission (Kim et al., 2018). However, the direction of this association is unclear. In other words, it is unclear if antipsychotic-related antidopaminergic effects lead to decreased dopaminergic activity that is then associated with iron depletion, or whether baseline iron deficiency interplays with antipsychotic effects resulting in motor symptoms. Based on our findings, iron supplementation may be indicated in the acute treatment phase, likely in the subgroup of patients at highest risk for akathisia, who could be the subgroup with pathological iron homeostasis. However, clinical data remain highly limited (Cotter and O'Keeffe, 2007; Gold and Lenox, 1995) and additional studies are needed to substantiate this hypothesis.

Based on the meta-regression analyses, none of the available moderators or mediators essentially contributed to the heterogeneity of iron blood levels. However, one study reported higher iron levels in males with akathisia compared to females (Nemes et al., 1991). Apart from physiological differences, a previous study reported antipsychotic-related iron level decrease in men, but not in women over a period of 8 weeks (Chen et al., 2018), in contrast to the evidence of Nemes and co-workers (Nemes et al., 1991), although Chen et al did not assess akathisia (Chen et al., 2018). Thus, sex-related patterns of antipsychotic-effects on iron homeostasis and the risk for akathisia need to further be investigated.

Previous literature has suggested dose-dependent patterns for akathisia (Salem et al., 2017). However, our evidence did not detect a differential antipsychotic dose-dependent effect on iron level patterns in akathisia patients. Nevertheless, as studies did not specify the various types of antipsychotic treatment, no further conclusions on this finding can be drawn. Moreover, not all studies reported these data, and the included dosages were daily averages and not cumulative dosages. Cumulative dosages might be a more suitable surrogate when addressing antipsychotic-dose effects (Modestin et al., 2000), but data were not available. Future trials addressing antipsychotic dose-effects will also need to stratify for the profiles

of patients, given the higher prevalence of iron deficiency in older aged people and in women (Coad and Pedley, 2014; Fairweather-Tait et al., 2014).

Inferences on iron status also require concurrent measurement of additional markers to iron measurements, such as ferritin, transferrin and TIBC (Wick et al., 2011). Nevertheless, differences in ferritin, transferrin and TIBC were not significant between patients with versus without akathisia, but data were limited and we cannot exclude a type II error. Thus, it is premature to draw conclusions on the relationship between akathisia and iron transport or storage in patients with akathisia. Patients with akathisia displayed lower ferritin levels compared to patients without akathisia, a difference that was only statistically significant in the fixed-effect model, but not significant in the random-effects model. Although the notion of decreased ferritin levels would tie in well with the concept of latent or acute iron store depletion (Hofmann et al., 2000), our findings marginally support that relationship. Specifically, ferritin differences between patients with and without akathisia reached statistical significance only in one of the included studies (Kuloglu et al., 2003). Kuloglu and associates provided some discussion on that finding using the long-term inpatient status of patients with akathisia as a potential explanation (Kuloglu et al., 2003). More data for ferritin are necessary to provide a clearer overview on iron storage in patients with akathisia.

Evidence for the involvement of iron transport in patients with akathisia, as reflected by patterns for transferrin and TIBC levels, were not particularly supportive, as findings were negative; yet the number of studies and patients were the smallest in these comparisons. Moreover, the large heterogeneity raises concerns when interpreting these findings, indicating that other factors not accounted for in our analyses are related to akathisia and iron homeostasis. For example, this heterogeneity may be linked to the variance of the analytical methods applied for the measurement of the iron status markers, but may also relate to other biological and clinical correlates of iron homeostasis and akathisia.

Results of this study need to be interpreted within its limitations. First, these include foremost the still small number of studies and patients that could be included in this meta-analysis. Since the significant finding regarding lower iron levels in patients with akathisia was observed in the analysis with the largest number of studies and patients, and the finding of lower ferritin levels at least in the fixed-effect model was found in the second largest number of studies and patients, we cannot exclude a type II error for the negative random-effects model findings in transferrin, ferritin and TIBC. Second, antipsychotic treatment that has differential risk for akathisia (Demyttenaere et al., 2019; Martino et al., 2018) was not detailed. Third, results were highly heterogeneous, very likely reflecting heterogeneous samples, such as in terms of antipsychotic doses, as well as methodological heterogeneity, limiting the certainty of the meta-analytic evidence. Fourth, information was mostly missing to grade the studies as high quality, an assessment only achieved by one of the ten studies. Fifth, we restricted our analyses to cross-sectional studies, but follow-up data on iron metabolism status in relationship to akathisia status in antipsychotic-treated patients are unfortunately too scarce to be meta-analyzed (Juncal-Ruiz et al., 2017; Sachdev and Loneragan, 1991). Sixth, three of the ten studies did not adjust the group comparisons for demographic and antipsychotic dose differences between study groups. Seventh, a large study that did not replicate the iron differences between patients with versus without akathisia could not be included in the meta-analysis due to failure to extract meta-analyzable data (Barnes et al., 1992). The authors were contacted, but data were no longer available, given the age of the study. Eighth, due to lack of specific data for any other diagnostic group,

subgroup analyses by diagnosis were only possible for schizophrenia-spectrum disorders. Finally, the number of moderator and mediator variables that could be examined in the meta-regression was small. In fact, one of the included studies did not report using any akathisia rating scale to group patients into those with vs. without akathisia (Horiguchi, 1991). However, although, clearly, more data are needed, the current meta-analysis is the first to comprehensively assess the relationship between iron metabolism markers and akathisia status in antipsychotic-treated patients, indicating that deficient iron levels may be implicated in the pathophysiology of akathisia.

In summary, results of this first meta-analysis of the relationship between iron homeostasis markers and akathisia in antipsychotic-treated patients emphasizes the complexity of the potential role of iron homeostasis in the risk for akathisia. Patients experiencing akathisia may have lower iron levels compared to patients without akathisia. Available data for other iron markers are currently still too limited to make conclusive statements. No differences were reported for transferrin and TIBC, whereas for ferritin one of the applied models reported lower levels in patients with akathisia. Cross-sectional and, especially, prospective studies focusing on the dynamic course of the interaction between iron status alterations and akathisia are required to shed additional light on the interaction between iron homeostasis and akathisia risk in antipsychotic-treated patients. Future research also needs to put more emphasis on unravelling the role of relevant clinical factors, such as acute versus chronic akathisia, duration of antipsychotic-exposure, antipsychotic type and dose. A better understanding of these factors and of biological underpinning could contribute to predicting, preventing, and potentially treating antipsychotic-related akathisia.

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Conflicts of interest

Drs. Schoretsanitis, Nikolakopoulou and Guinart have nothing to disclose.

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Table 1 Characteristics of included studies (in alphabetical order).

Author, year	Total n	Group	n	Akathisia rating scale	Age, years (SD)	%♀	Diagnosis	Duration of illness (SD), years	Duration of treatment[1] (SD), years	CPZE dosage (SD)	Group Comparison adjusted for demographic and CPZE group differences	Iron blood levels (SD), mg/dl	Ferritin blood levels (SD), ng/ml	Transferrin blood levels (SD), mg/dl	TIBC (SD), μg/dl
Barton, 1990	30	Chronic akathisia	15	Akathisia rating scale[2]	51.5	33.3	NP	27.8	18.5 (4.8)	942.5	Yes	100.1 (35.3)	43.76 (25.79)	NP	246.8 (66.29)
		Non-akathisia	15		51.8	33.3		24.4	16.1 (4.4)	999.0		91.2 (30.2)	73.07 (42.63)	NP	260.72 (49.61)
Brown, 1987	26	Chronic akathisia	13	Akathisia rating scale[2]	60.1 (11.9)	61.5	NP	25.0 (10.1)	17.0 (1.5)	387 (241.6)	Yes	58.1 (26.3)	136.2 (202.13)	NP	314.36 (59.35)
		Non-akathisia	13		57 (9.0)	61.5		21.4 (11.9)	18.4 (2.7)	361 (472.3)		103.6 (40.1)	83.73 (82.37)	NP	281.39 (37.73)
Hofmann, 2000	56	Acute akathisia	33	HAS[3]	38.5 (14.5)	63.6	54.5% SZ, 30.3% SA, 12.1% AD	8.5 (8.2)	NP	1031 (651)	Yes	88.52 (40)	56.94 (39.54)	NP	NP
		Non-akathisia	23		34 (9.6)	43.5	56.5% SZ, 39.1% SA, 4.3% AD, 3% other	7.9 (6.5)	NP	818 (517)		114.74 (55.1)	102.13 (87.73)	NP	NP
Horiguchi, 1991	27	Chronic akathisia	10	NP	33[4]	11.1[4]	83.3% SZ, 5.6% AD, 5,6% SA, 5.6% other	NP	6[4]	NP	No	79.6 (28.7)[4]	NP	NP	NP
		Non-akathisia or -dystonia	17		29	0	94.1% SZ, 5.9% AD	NP	5.8	NP		126.9 (20.2)	NP	NP	NP
Kuloglu, 2003	60	Chronic akathisia	30	BARS[5]	42.0 (4.1)	46.7	100% SZ	17.4 (2.8)	14.2 (1.91)	1013 (241)	Yes	68.9 (9.2)	53.37 (7.92)	225.13 (13.34)	404.3 (20.91)
		Non-akathisia	30		39.8 (4)	46.7		17.6 (5.1)	13.8 (2.21)	987 (278)		81.3 (10.6)	65.94 (11.08)	217.28 (16.36)	390.15 (15.16)

(*continued on next page*)

Table 1. Characteristics of included studies (in alphabetical order)

Table 1 *(continued)*

Author, year	Total n	Group	n	Akathisia rating scale	Age, years (SD)	%♀	Diagnosis	Duration of illness (SD), years	Duration of treatment[1] (SD), years	CPZE dosage (SD)	Group Comparison adjusted for demographic and CPZE group differences	Iron blood levels (SD), mg/dl	Ferritin blood levels (SD), ng/ml	Transferrin blood levels (SD), mg/dl	TIBC (SD), μg/dl
Nemes, 1991	50	Chronic Akathisia	25	Akathisia rating scale[2]	44.8 (11.2)	4	92% SZ 8% BD	19.5 (11.1)	NP	1277 (1333)	No	83.3 (37.1)	116.3 (80.5)	NP	NP
		Non-akathisia	25		44.8 (12.1)	4		19.4 (12.4)	NP	817 (964)		78.8 (27.3)	93.5 (73.1)	NP	NP
O'Loughlin 1991	30	Acute akathisia	6	Akathisia rating scale[2]	NP	NP	56.7% BD, 43.3% SZ	NP	NP	NP	No	112.8	NP	200.0	NP
		Non-akathisia	24		NP	NP		NP	NP	NP		128.99	NP	260.0	NP
Sachdev, 1994	44	Tardive akathisia	14	BARS[5]	40.8 (10.2)	35.7	100% SZ	NP	14.3 (8.4)	723.2 (596.5)	Yes	99.05 (40.8)	115.06 (115.4)	311.43 (50.0)	NP
		Non-akathisia or -dyskinesia	30		38.7 (8.4)	33.3		NP	14.3 (9.2)	620.2 (801.8)		98.33 (38.5)	139.5 (193.3)	320.0 (100.0)	NP
Soni, 1993	44	Chronic akathisia	22	Akathisia rating scale[2]	NP	NP	100% SZ	22.8 (14.9)	NP	NP	Yes	87.68 (37.4)	71.4 (74.7)	NP	330.75 (51.29)
		Non-akathisia	22		NP	NP			NP	NP		93.82 (34.9)	51.6 (51.1)	NP	323.49 (11.84)
Vallés, 1992	28	Chronic akathisia	14	Akathisia rating scale[2]	NP	NP	100% SZ	NP	NP	NP	Yes	84.88 (27.9)	NP	NP	289.96 (60.34)
		Non-akathisia	14		NP	NP		NP	NP	NP		109.46 (40.2)	NP	NP	313.43 (48.61)
Total	**395**	**Akathisia**	**182**	**Akathisia rating scale: *N* = 6; BARS: *N* = 2; HAS: *N* = 1; NP: *N* = 1**	**42.16±9.1**	**34.5**	**SZ: 85.6% NP: 13.9% BD: 6.05% SA: 5.8% AD: 2.0% Other: 0.6%**	**18.32 ±6.3**	**12.9 ± 5.54**	**875.05 ±271.6**	**Yes: N-=3; No: *N* = 7**	**93.34 ±18.21**	**84.4 ± 31.77**	**258.75 ±50.5**	**321.03 ±47.36**
		Non-akathisia	**213**												

♀ women, AD: affective disorders; BARS: Barnes Akathisia Scales, CPZE: chlorpromazine, HAS: Hillside Akathisia Scales, n: number of patients, NP: not provided, SA: schizoaffective disorders, SD: standard deviation, SZ: schizophrenia, TIBC: total iron-binding capacity.

[1] Refers to antipsychotic treatment.

[2] Developed by Brown et al. (Brown et al., 1987). Except for one study that used a threshold of 9 to define akathisia (Vallés et al., 1992), all other studies used a threshold of 10.

[3] No threshold of HAS score was provided for the definition of akathisia.

[4] Refers to a mixed group of 10 patients with akathisia and 8 patients with dystonia.

[5] A BARS global score >2 was considered for the definition of akathisia.

Figure 1. Iron blood levels (mg/dL) in patients with vs. without akathisia.

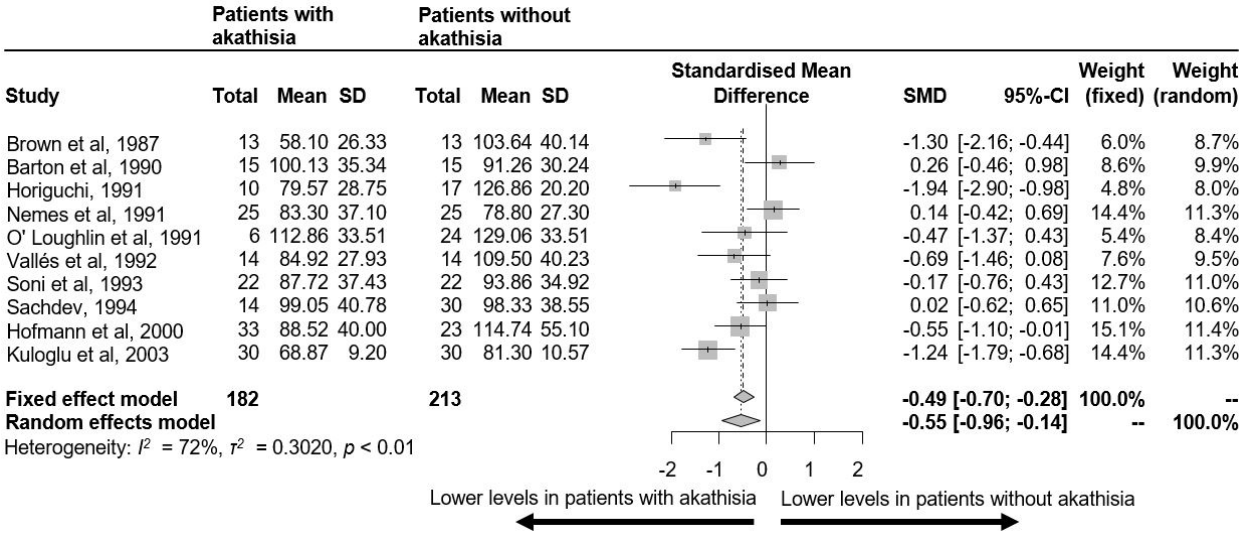

Figure 2. Ferritin blood levels (ng/mL) in patients with vs. without akathisia.

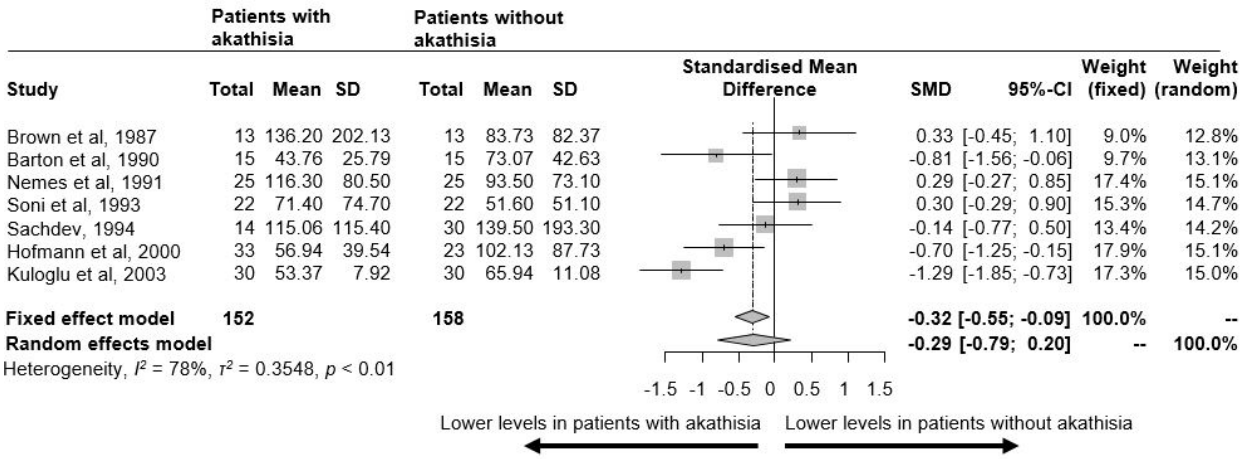

Figure 3. Transferrin blood levels (mg/dL) in patients with vs. without akathisia.

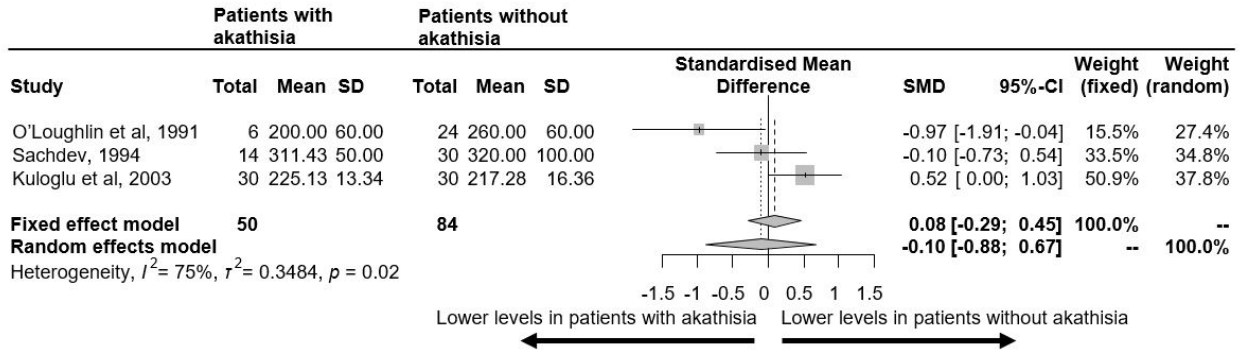

Figure 4. Total iron-binding capacity (TIBC) (µg/dL) in patients with vs. without akathisia.