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## Schizophrenia Research

journal homepage: [www.elsevier.com/locate/schres](http://www.elsevier.com/locate/schres)

## Association between C-reactive protein levels and antipsychotic treatment during 12 months follow-up period after acute psychosis

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## ARTICLE INFO

## Keywords:

Psychosis

Schizophrenia

Antipsychotic drugs

Inflammation

C-reactive protein

## ABSTRACT

**Background:** A potential role of inflammatory pathways in the pathology of schizophrenia has been suggested for at least a subgroup of patients. Elevated levels of the inflammatory marker C-reactive protein (CRP) have been observed, with associations to pathogenesis and symptoms. The current evidence regarding effects of antipsychotics on CRP levels is ambiguous.

**Objectives:** To examine and compare the influence on CRP levels of three pharmacologically diverse new generation antipsychotics during a one-year follow-up in schizophrenia spectrum disorder.

**Methods:** In a multicenter, pragmatic and rater-blinded randomized trial, the effects of amisulpride, aripiprazole and olanzapine were compared in 128 patients with schizophrenia spectrum disorder. All had positive symptoms of psychosis at study entry. Clinical and laboratory assessments including the measurement of CRP levels were conducted at baseline, and 1, 3, 6, 12, 26, 39, and 52 weeks thereafter.

**Results:** For all antipsychotic drugs analysed together, there was an increase in CRP levels during the one-year follow-up. Aripiprazole, as opposed to amisulpride and olanzapine, was associated with a reduced CRP level after one week, after which the CRP level caught up with the other drugs. Compared to those previously exposed to antipsychotic drugs, antipsychotic-naïve patients had lower CRP levels at all follow-up time points, but with the same temporal patterns of change.

**Conclusion:** Treatment with amisulpride, aripiprazole and olanzapine showed different effects on CRP levels in patients with schizophrenia spectrum disorders, modified by previous antipsychotics exposure status. This finding suggests that antipsychotic drugs may vary with respect to their influence on pro-inflammatory pathways.

**Trial registration:** ClinicalTrials.gov ID: NCT01446328; URL: <http://www.clinicaltrials.gov/>.

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<https://doi.org/10.1016/j.schres.2022.01.049>

Received 5 April 2021; Received in revised form 4 January 2022; Accepted 22 January 2022

Available online 4 February 2022

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## 1. Introduction

Schizophrenia spectrum disorders (SSD) are characterized by combinations of positive, negative, cognitive, mood and motor symptoms of varying complexity and chronicity (Tandon et al., 2009). Different pathophysiological hypotheses have been proposed, and the roles of inflammation and immune system disturbances have received particular attention in recent years based on converging evidence from different areas of research (Horvath and Mirnics, 2014; Ripke et al., 2013; Schizophrenia Working Group of the Psychiatric Genomics, 2014; Stefansson et al., 2009; Uptegrove et al., 2014). C-reactive protein (CRP), primarily induced by interleukin-6 (IL-6) during the acute phase of inflammation or infection, is a reliable marker of inflammation (Castell et al., 1990; Marnell et al., 2005). CRP levels in the 3–10 mg/L range suggest low-grade inflammation, while CRP levels >10 mg/L imply inflammation (Windgassen et al., 2011).

Elevated CRP levels have been associated with schizophrenia in general (Dickerson et al., 2013), as well as more specifically with an increased risk for schizophrenia (Nimgaonkar et al., 2018), higher symptom severity (Fan et al., 2007), treatment resistance (Horsdal et al., 2017), negative symptoms (Boozalis et al., 2017), depressive symptoms (Faugere et al., 2018), and cognitive dysfunction (Dickerson et al., 2007; Jacomb et al., 2018; Johnsen et al., 2016). A systematic review reported that elevated CRP levels in schizophrenia mainly correlated with severity of illness during exacerbations, and that CRP levels seemed to be associated with catatonic features, negative symptoms and aggressiveness (Orsolini et al., 2018). Further, an elevated baseline CRP level has been suggested as a biomarker for a poor clinical prognosis in stable patients with schizophrenia (Gonzalez-Blanco et al., 2018).

Antipsychotic drugs (AP), mainstays in schizophrenia treatment may also be associated with various changes of inflammatory markers (Chu et al., 2018; Gurung et al., 2018; Henderson et al., 2009; Joseph et al., 2015; Kroken et al., 2014; Lee et al., 2018; Yuan et al., 2018). Although it has been assumed that AP have a net anti-inflammatory effect (Romeo et al., 2018), the literature is mixed and partly conflicting. Metabolic adverse effects including weight gain, dyslipidemia and glycemic dysregulation from APs may confound associations between (anti)inflammatory effects of APs and CRP. Most APs are associated with various degrees of weight gain, with olanzapine representing the worst and aripiprazole the most benign profile, with amisulpride in-between for most of the metabolic effects (Pillinger et al., 2020). Such differences between APs for their adverse metabolic impact including weight gain can at least partly be related to the drugs' different receptor affinities in the brain (Kaar et al., 2020). All currently used APs act as functional antagonists at dopamine D2/D3 receptors which is core to their antipsychotic efficacy (Howes et al., 2009; Kapur et al., 2000). Evidence also exists for disruption of dopamine related reward pathways in patients treated with AP, which may lead to changes in food consumption and weight gain (Grimm et al., 2017). Amisulpride selectively impacts the dopaminergic system, whereas the other APs bind to different extradopaminergic systems as well, including serotonin 5-HT<sub>2A</sub>, histamine H<sub>1</sub>, and muscarinic M receptors (Kaar et al., 2020), that have all been associated with metabolic dysregulation (Kroeze et al., 2003). Interestingly, aripiprazole, a dopamine partial agonist with little or no histaminergic or serotonergic antagonism shows low risk of weight gain and metabolic side effects (Rummel-Kluge et al., 2010). Furthermore, contrary to other APs, aripiprazole has been associated with low CRP levels (<1 mg/L) (Fond et al., 2018).

The aim of this study was to investigate, in a clinically representative sample of SSD patients with positive symptoms of psychosis, whether differential effects on CRP levels exist between three first-line new generation antipsychotic drugs (NGAP) with different pharmacological profiles: amisulpride, aripiprazole and olanzapine.

## 2. Patients and methods

### 2.1. Study design

The study is part of the Bergen-Stavanger-Innsbruck-Trondheim (BeStInTro) trial, see our previous publication for further details (Johnsen et al., 2020). The study had a pragmatic, head-to-head, rater-blind and randomized design with assessments at baseline and at weeks 1, 3, 6, 12, 26, 39 and 52 thereafter. Study drugs were amisulpride (50–1200 mg/day), aripiprazole (5–30 mg/day), and olanzapine (2.5–20 mg/day), taken as oral tablets according to the Summary of Product Characteristics (SPC) (<https://www.medicines.org.uk/emc>). The randomization procedure created a random sequence of the study drugs for each participant, see our previous publication for further details (Johnsen et al., 2020). The first study drug in the sequence defined the randomization group and was the basis of the intention-to-treat (ITT) analyses. If the first study drug in the sequence could not be used for reasons of effectiveness and/or tolerability, the next drug in the sequence was offered. The actually chosen study drug in the sequence was the basis of per protocol (PP) analyses. Initiation, dosing and any subsequent changes or discontinuation of medication were left to the discretion of the attending physician or psychiatrist. Concomitant medications were permitted to resemble usual clinical practice, with the exception of additional AP. However, cross-titration was permitted in case of AP switches.

The study was approved in Norway by the Regional committees for Medical and Health Research Ethics, and by the Norwegian Medicines Agency; in Austria by the Etikkommission der Medizinische Universität Innsbruck, and the Austrian Federal Office for Safety in Health Care (BASG). All participants received written and verbal information, and provided written informed consent before study inclusion.

#### 2.1.1. Clinical sample

The participants were enrolled at three Norwegian sites: in Bergen, Stavanger and Trondheim, and one Austrian site in Innsbruck. The inclusion criteria were: (1) age  $\geq 18$  years; (2) positive symptoms of psychosis based on a score  $\geq 4$  on at least one of the following items of the Positive And Negative Syndrome Scale (PANSS) (Kay et al., 1987) delusions (P1), hallucinations (P3), grandiosity (P5), suspiciousness/persecution (P6) and unusual thought content (G9); and (3) a diagnosis within the SSD (F20-F29) according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) (World Health Organization, 2007). The exclusion criteria were: (1) indication for non-oral administration of AP; (2) inability to understand the native language; (3) pregnancy or lactation; and (4) hypersensitivity to study medications. The first participant was included October 20th 2011, and the last follow-up visit for the last included participant was December 21st 2017.

#### 2.1.2. Clinical and biochemical assessments

Patients were assessed at all 8 visits with the PANSS structured clinical interview (SCI-PANSS), the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1990), the Clinical Global Impression – severity of illness scale (CGI-S) (Guy, 1976), the clinical drug and alcohol use scales (CDUS/CAUS) (Mueser et al., 1995), and the Global Assessment of Functioning (GAF) (American Psychiatric Association, 2000). In line with a previous publication from our group (Johnsen et al., 2016), the cardiovascular disease (CVD) risk score was calculated based on the International Diabetes Federation cut-off values for the definition of metabolic syndrome (Federation, 2020).

Each risk factor (obesity, increased triglycerides, reduced HDL cholesterol, elevated blood pressure, and increased fasting plasma glucose) was dichotomized as absent (0) or present (1), resulting in a CVD risk score between 0 and 5. Blood samples were collected in the fasting state between 08:00 and 10:00 a.m. CRP levels were measured by the Tina-quant C-reactive protein (Latex) method from Roche Modular

PP®, which detected CRP levels > 0.10 mg/L. In order to exclude underlying acute inflammation or infection, patients with baseline CRP values  $\geq 10$  mg/L were removed from the analyses (Nehring and Patel, 2019; Windgassen et al., 2011).

### 3. Statistical analyses

Observed data at baseline were analysed using SPSS Statistics for Windows, Version 24.0 (IBM Corp). Mplus version 8 was used to estimate CRP level and change over time (Muthén and Muthén, 2017). Potential deviations from normal distribution were handled by the robust maximum likelihood estimator (MLR). Linear change was first tested and evaluated with standard fit measures. A satisfactory fit was indicated by statistically non-significant chi-square, normed fit index (NFI), Tucker-Lewis index (TLI) > 0.95, and root mean square error of approximation (RMSEA) < 0.05 (close fit), < 0.08 (fair fit) or < 0.10 (mediocre fit), including confidence intervals and probability of close fit in the population (Kline, 2016). As a linear model did not fit data very well, change was estimated as increasing time intervals with reference to the baseline score (0–1, 0–3, 0–6 weeks and so on). In order to estimate these models and time specific residuals the slope variance had to be fixed (Heck and Thomas, 2015). Lag one residual relations were estimated in order to account for stability not clarified by the trends in the model (Newsom, 2015). The model fit was at an acceptable level ( $\chi^2 = 32.08$ ,  $df = 19$ ,  $p = 0.031$ , CFI = 0.94, TLI = 0.91, RMSEA = 0.073, RMSEAc.i. = 0.023–0.116, RMSEAclose fit = 0.18).

Predictors were then entered as two contrast code variables analysing the statistical effect of aripiprazole and olanzapine in relation to amisulpride. Amisulpride was, as in a previous publication (Johnsen et al., 2020), chosen as the reference drug due to its selective affinity for dopaminergic receptors, and to limit the number of comparisons. Aripiprazole and olanzapine were compared as post-hoc analyses. The primary analyses were PP analyses based on the actual study drug chosen. These were supplemented by secondary ITT analyses based on randomization groups. Both strategies of analyses have pros and cons. The main advantage of PP analyses is that treatment effects on CRP levels (i.e. a biological marker) may be more closely linked to the study drug used. However, the breach of randomization makes PP analyses more susceptible to selection bias and confounding of associations between study drug and effect. The main advantage of ITT analyses is that randomization protects against selection bias between groups. Disadvantages include that any differences between groups may be diluted because the randomization groups are “contaminated” by participants choosing a drug other than the first one in the randomization sequence. Prediction of changes in CRP level was adjusted for baseline CRP values. The final model included the effect of medication, being AP-naïve as no previous exposure to AP, the number of weeks on the drug first started, and the two interaction terms: medication and weeks, and medication and being AP-naïve. This model also adjusted for smoking, gender, body mass index (BMI), and CDUS, as BMI and tobacco smoking influence the CRP level (Costello et al., 2013; Ghazavi et al., 2013; Gonçalves et al., 2011; Kushner et al., 2006; Pearson et al., 2003; Tibuakuu et al., 2017), and might confound associations between CRP, schizophrenia, and AP treatment. The CVD risk score was also intended as one of the covariates; however, due to mean equal zero and no variance in the medication naïve group, this variable was left out of the model.

The differences between being medication naïve before study inclusion, and having had previous exposure to antipsychotics, were analysed within a multi-sample framework (Kline, 2016). In order to make the model as parsimonious as possible, the parameter values for the adjustment variables were constrained to be equal over the two samples (regression weights, variances, and residuals). This keeps precision of the estimates at a similar level as in single sample analyses. Thus, the reference group was those previously exposed to AP, fixed at mean level of the adjustment variables and receiving amisulpride. Weeks on first medication and baseline BMI were mean centered in

order to change the interpretation of the medication effects at mean levels of weeks. The level of statistical significance was set at p-value below 0.05.

### 4. Results

In total, 144 patients were randomized at baseline, where 24 patients (16.7%) chose a study drug other than the first one in the randomization sequence, with no statistically significant difference among the ITT groups (chi-square test  $p = 0.120$ ).

For the present project, nine patients were excluded due to serum CRP levels  $\geq 10$  mg/L, and seven were excluded due to lack of any CRP level measurements. There were no statistically significant differences between the three randomization groups regarding the aforementioned excluded patients (chi-square test  $p = 0.070$ , and  $p = 0.125$  respectively). The net sample consisted of 128 patients. The inclusion process and trial profile, including a detailed dropout overview throughout the study are displayed in Fig. 1. The total dropout rate was about 46%. About two thirds of the sample were inpatients (Johnsen et al., 2020). The mean (SD) age at baseline was 31.9 (12.8) years ( $p = 0.808$ ), and 65% of patients were male. One patient randomized to amisulpride had mild symptoms of upper respiratory tract infection. For more demographic and clinical information see Table 1.

#### 4.1. Level and change in CRP

For all groups together, the estimated mean CRP level changed from 1.48 mg/L at baseline to 2.75 mg/L after 52 weeks, and reached a top level of 3.23 mg/L after 39 weeks. The results showed statistically significant increases from baseline in all intervals, from the 3rd week onwards (Table 2).

#### 4.2. The effect of different study drugs on changes in CRP

Table 3 presents PP and ITT results for the three study medications. In both PP and ITT results, the reference medication amisulpride was estimated to have the highest CRP level after 39 weeks. In PP analyses, the CRP level increased during the 0–1 and 0–26 week interval in this group, while the aripiprazole group showed significantly less increase, or even a decrease in CRP levels in both the 0–1 and 0–3 week intervals. The ITT analyses showed a decrease in the 0–3 week interval. See also Fig. 2.

#### 4.3. The full prediction model – PP and ITT analyses

The main effects of AP and interaction effects of being AP-naïve or previously medicated, adjusted for the covariates of gender, baseline BMI, smoking and CDUS are shown in Table 4 and Fig. 3.

The PP analyses showed a significant increase of CRP levels in the previously AP exposed patients in the amisulpride group during the 0–26 week interval. Furthermore, a significant reduction of the CRP level in the AP-naïve patients in this group was shown during the 0–1 week interval. However, previously AP exposed patients of the aripiprazole group showed significant differences in CRP level changes in contrast to the amisulpride group. The CRP levels were reduced in the 0–1, 0–3, and 0–26 week intervals, while an increase was observed in the 0–52 week interval. Patients previously exposed to AP receiving olanzapine showed a significant decrease in CRP levels during the 0–26 week interval.

Regarding covariates and interactions outcomes, a positive association between BMI and CRP levels was present at baseline ( $b = 0.11$ ,  $p = 0.002$ ), and those with higher BMI at baseline ( $b = 0.21$ ,  $p = 0.049$ ) had less CRP level reduction. In the previously medicated group, smoking at baseline was associated with less CRP level reduction in the 0–39 week interval ( $b = 1.66$ ,  $p = 0.049$ ). There were statistically significant contributions from duration of study drug treatment in some subgroup

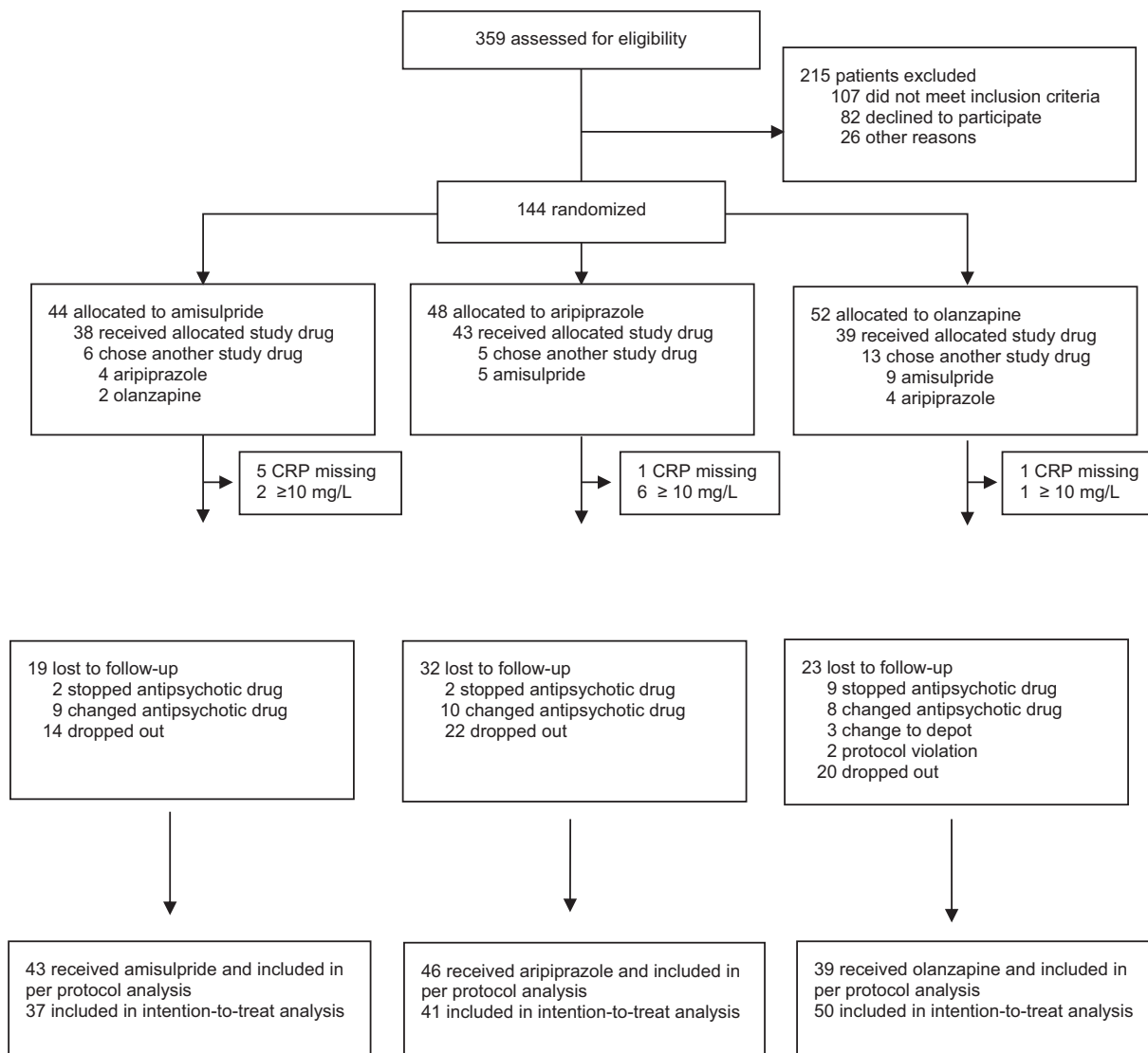


Fig. 1. Trial profile.

CRP missing = Not available CRP measurements at any time points.

mg/L = milligram/liter.

Protocol violation = use of dosage above upper limit according to the study protocol.

analyses, including more pronounced CRP level reduction in the 0–6 week interval in the olanzapine users medicated for longer time (Olanzapine x time:  $b = -0.14$ ,  $p = 0.041$ ). In the total study period (0–52 weeks), greater CRP level reduction was found in the olanzapine group for those medicated for a longer time ( $b = -0.12$ ,  $p = 0.014$ ). Furthermore, the aripiprazole group had less CRP level reduction, when medicated for a shorter period ( $b = 0.35$ ,  $p < 0.001$ ). Finally, a gender difference was present in the 0–26 week interval as CRP level reduction was greater for males than females ( $b = 1.21$ ,  $p < 0.001$ ).

The results based on ITT analyses were similar to those of the PP results (Table 4).

Use of anti-inflammatory drugs that could potentially influence CRP levels during the study were as follows: Non-steroid anti-inflammatory drugs (NSAIDs) were used at the different assessment points by a total of 4 (one week assessment point), 3 (three weeks), 1 (six weeks), 2 (12 and 26 weeks), 3 (39 weeks), and zero (52 weeks) patients, with no significant differences between the study groups except after three weeks with three users of NSAIDs in the amisulpride group, and none in the other groups (Pearson Chi Square:  $p = 0.023$ ). Locally administered steroids (aerosols) were used by two (1 week), one (three weeks), four (six

weeks), 3 (12 weeks), 1 (26 and 39 weeks), and zero (52 weeks) patients, with no statistically significant differences between the study drug groups (Pearson Chi Square:  $p > 0.384$  for all).

### 5. Discussion

The main findings of this study were that first-line NGAP are associated with change of CRP levels during the initial treatment phase of SSD with positive symptoms in a differential way, and that the relationship between the AP and CRP levels appears to be partly dependent of previous exposure to AP or not. Aripiprazole was associated with a statistically significant reduction of CRP level during the first 3 weeks of treatment, whereas olanzapine and amisulpride were not. However, we found a modest increase of CRP levels from the 3rd week onwards for the whole group.

These findings are consistent with a previous study, in which aripiprazole was the only AP associated with low CRP levels compared to other APs, including quetiapine, olanzapine, amisulpride, clozapine, loxapine, risperidone, zuclopenthixol, paliperidone, and cyamemazine (Fond et al., 2018). Another aripiprazole study, with a 4 weeks follow-up

**Table 1**  
Demographics and other relevant baseline information.

|                          | All<br>N = 128<br>n/% | Amisulpride<br>N = 43<br>n/% | Aripiprazole<br>N = 46<br>n/% | Olanzapine<br>N = 39<br>n/% | Medication differences p-value |
|--------------------------|-----------------------|------------------------------|-------------------------------|-----------------------------|--------------------------------|
| Male gender              | 82 (65%)              | 20 (48%)                     | 35 (76%)                      | 27 (69%)                    | 0.016                          |
| Diagnosis                |                       |                              |                               |                             |                                |
| Schizophrenia            | 70 (56%)              | 24 (57%)                     | 26 (57%)                      | 20 (53%)                    | 0.909                          |
| Schizotypal              | 2 (2%)                | 1 (2%)                       | 0 (0%)                        | 1 (3%)                      | 0.555                          |
| Delusional disorder      | 21 (17%)              | 6 (14%)                      | 8 (17%)                       | 7 (18%)                     | 0.872                          |
| Brief psychotic disorder | 17 (14%)              | 8 (19%)                      | 5 (11%)                       | 4 (11%)                     | 0.434                          |
| Schizo-affective         | 8 (6%)                | 3 (7%)                       | 3 (7%)                        | 2 (5%)                      | 0.941                          |
| Other                    | 1 (1%)                | 0 (0%)                       | 1 (2%)                        | 0 (0%)                      | 0.416                          |
| Unspecified              | 7 (6%)                | 0 (0%)                       | 3 (7%)                        | 4 (11%)                     | 0.114                          |
| Antipsychotic-naïve      | 50 (39%)              | 14 (33%)                     | 20 (44%)                      | 16 (41%)                    | 0.548                          |
| Smoking                  | 76 (65%)              | 24 (60%)                     | 30 (71%)                      | 22 (63%)                    | 0.529                          |
| Abuse/dependence         |                       |                              |                               |                             |                                |
| Alcohol                  | 11 (9%)               | 2 (5%)                       | 7 (16%)                       | 2 (6%)                      | 0.142                          |
| Drugs                    | 25 (20%)              | 7 (17%)                      | 11 (26%)                      | 7 (20%)                     | 0.622                          |
| Infection                | 1 (0.07%)             | 0                            | 0                             | 1                           | 0.830                          |
| Autoimmune disease       | 8 (6%)                | 2                            | 1                             | 5                           | 0.428                          |
| Oral steroids            | 0                     |                              |                               |                             |                                |
| Non-oral steroids        | 2 (1%)                | 0                            | 1                             | 1                           | 1.000                          |
| NSAIDs                   | 5 (3%)                | 2                            | 2                             | 1                           | 0.733                          |

|                | All<br>N = 128<br>Mean (SD) | Amisulpride<br>N = 43<br>Mean (SD) | Aripiprazole<br>N = 46<br>Mean (SD) | Olanzapine<br>N = 39<br>Mean (SD) | Medication differences p-value |
|----------------|-----------------------------|------------------------------------|-------------------------------------|-----------------------------------|--------------------------------|
| PANSS total    | 77.8 (16)                   | 79.5 (18.7)                        | 77.9 (13.8)                         | 75.9 (15.2)                       | 0.614                          |
| PANSS positive | 21.1 (4.8)                  | 21.3 (4.9)                         | 21.5 (5.0)                          | 20.3 (4.5)                        | 0.477                          |
| PANSS negative | 17.6 (6.1)                  | 17.6 (6.6)                         | 17.5 (5.5)                          | 17.6 (6.2)                        | 0.997                          |
| PANSS general  | 39.1 (8.7)                  | 40.5 (9.6)                         | 38.8 (8.2)                          | 38.0 (8.1)                        | 0.404                          |
| CGI            | 5.0 (0.8)                   | 4.9 (0.9)                          | 5.0 (0.7)                           | 5.1 (0.7)                         | 0.795                          |
| GAF-F          | 36.0 (8.5)                  | 35.7 (7.1)                         | 35.2 (6.9)                          | 37.1 (11.1)                       | 0.713                          |
| CDSS           | 6.7 (5.2)                   | 8.0 (5.6)                          | 5.6 (4.7)                           | 6.6 (5.1)                         | 0.104                          |
| BMI            | 25.1 (5.2)                  | 25.2 (5.9)                         | 26.4 (4.8)                          | 23.4 (4.5)                        | 0.053                          |
| CRP            | 1.5 (1.8)                   | 1.2 (1.7)                          | 1.8 (1.8)                           | 1.4 (1.9)                         | 0.298                          |

Notes: N = number in total sample, n = number with characteristics, SD = standard deviation, m = mean, PANSS = the Positive and Negative Syndrome Scale, CDSS = the Calgary Depression Scale for Schizophrenia, GAF-F = Global Assessment of Functioning-split version, functions scale, CGI = Clinical Global Impression, severity of illness scale, BMI = body mass index, CRP = C-reactive protein (mg/L).

Levene's test showed GAF-F to have different variances in the groups. Therefore, Welch test for group differences was used.

**Table 2**  
Estimated level and change in CRP.

| Time     | Changes from baseline |       |
|----------|-----------------------|-------|
|          | Mean                  | p     |
| Baseline | 1.48                  |       |
| 0–1      | 0.13                  | 0.299 |
| 0–3      | 0.60                  | 0.004 |
| 0–6      | 0.76                  | 0.011 |
| 0–12     | 1.20                  | 0.001 |
| 0–26     | 0.66                  | 0.002 |
| 0–39     | 1.57                  | 0.003 |
| 0–52     | 1.27                  | 0.007 |

Notes: CRP = C-reactive protein (mg/L); time = week; p = p-values.

in chronic schizophrenia patients, also showed a significant reduction in CRP levels (Sobis et al., 2015). As our study shows an initial decrease in CRP over the first 3 weeks on aripiprazole and then an increase, studies with a follow-up interval of only 4 weeks must be interpreted with caution.

Interaction analysis revealed that the initial CRP reduction in the aripiprazole group was driven by the subgroup previously exposed to AP. This potentially CRP lowering effect of aripiprazole in AP pre-exposed patients might reflect increased BMI and/or a corresponding pro-inflammatory state at baseline associated with earlier medication use, or pro-inflammatory effects associated with more advanced disorder, counteracted by the initiation of aripiprazole. AP might lead to metabolic changes, including weight gain, increased lipid levels and

**Table 3**  
Effect of antipsychotic medication on CRP adjusted for baseline CRP levels.

| Week       | ami <sup>o</sup> |          | ari <sup>a</sup> |                | ola <sup>b</sup> |       |
|------------|------------------|----------|------------------|----------------|------------------|-------|
|            | b <sub>0</sub>   | est.mean | b <sub>1</sub>   | b <sub>2</sub> |                  |       |
| <i>PP</i>  |                  |          |                  |                |                  |       |
| 0          | 1.50             | 1.50     | 0.00             |                |                  | 0.00  |
| 0–1        | 0.54*            | 2.08     | -0.98**          |                |                  | -0.41 |
| 0–3        | 0.53             | 2.30     | -0.98*           |                |                  | 0.38  |
| 0–6        | 0.43             | 2.51     | -0.45            |                |                  | -0.37 |
| 0–12       | 0.47             | 2.78     | -0.35            |                |                  | 0.01  |
| 0–26       | 1.06*            | 2.59     | -0.80            |                |                  | -0.73 |
| 0–39       | 0.57             | 2.83     | 0.31             |                |                  | 0.44  |
| 0–52       | 0.69             | 2.19     | 1.36             |                |                  | 0.78  |
| <i>ITT</i> |                  |          |                  |                |                  |       |
| 0          | 1.49             | 1.49     | 0.00             |                |                  | 0.00  |
| 0–1        | 0.35             | 1.91     | -0.67            |                |                  | -0.24 |
| 0–3        | 0.75             | 2.61     | -1.51**          |                |                  | -0.23 |
| 0–6        | -0.17            | 1.84     | 1.18             |                |                  | 0.24  |
| 0–12       | 0.22             | 2.50     | 0.48             |                |                  | 0.12  |
| 0–26       | 0.70*            | 2.17     | 0.03             |                |                  | -0.17 |
| 0–39       | 0.73             | 3.04     | -0.23            |                |                  | 0.10  |
| 0–52       | 1.09             | 2.69     | 0.12             |                |                  | 0.04  |

Notes: CRP = C- reactive protein (mg/L); ami<sup>o</sup> = reference medication, amisulpride, intercept (b<sub>0</sub>) level and estimated mean level at the end of each week interval (est.mean) adjusted for baseline level in CRP; ari<sup>a</sup> = aripiprazole versus amisulpride; ola<sup>b</sup> = olanzapine versus amisulpride; b = regression weights.

\* p < 0.05.

\*\* p < 0.01.

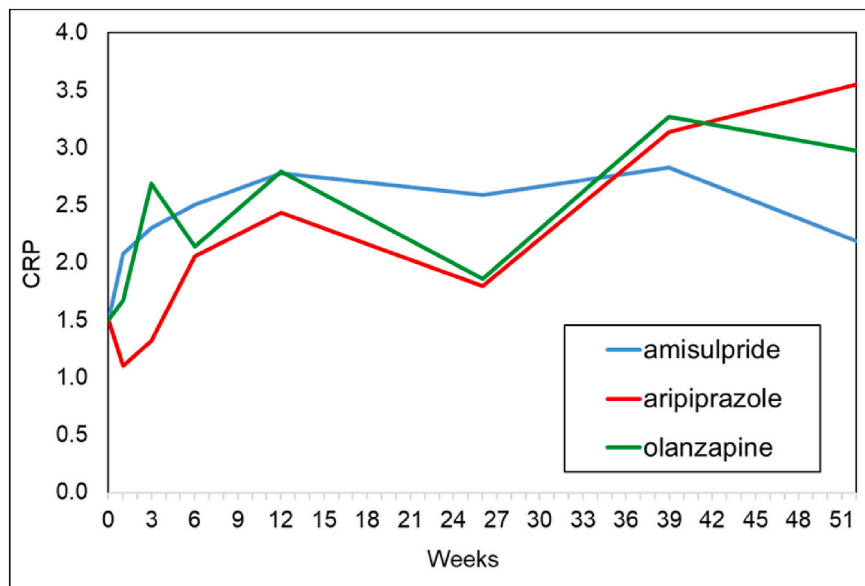


Fig. 2. Differences in estimated CRP levels over time per protocol. CRP = C-reactive protein (mg/L).

**Table 4**  
Estimated CRP levels predicted by aripiprazole and olanzapine with reference to level and change with amisulpride.

| Weeks      | Previously medicated group |                          |                          | Medication naïve group   |                          |                          |
|------------|----------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
|            | ami <sup>0</sup>           | ari <sup>a</sup>         | olan <sup>b</sup>        | ami <sup>0</sup>         | ari <sup>a</sup>         | olan <sup>b</sup>        |
|            | <i>b</i> <sub>0,G1</sub>   | <i>b</i> <sub>1,G1</sub> | <i>b</i> <sub>2,G1</sub> | <i>b</i> <sub>0,G2</sub> | <i>b</i> <sub>1,G2</sub> | <i>b</i> <sub>2,G2</sub> |
| <i>PP</i>  |                            |                          |                          |                          |                          |                          |
| 0          | 1.84***                    | –                        | –                        | 0.83*                    | –                        | –                        |
| 0–1        | 0.11                       | –1.80***                 | –0.38                    | –0.77*                   | 0.47                     | 0.13                     |
| 0–3        | 0.07                       | –1.16*                   | 0.31                     | –0.09                    | 0.01                     | 0.74                     |
| 0–6        | –0.85                      | 0.10                     | 0.57                     | –1.46                    | –0.74                    | 1.44*                    |
| 0–12       | 1.25                       | 0.55                     | –0.55                    | 0.54                     | 0.49                     | 4.58                     |
| 0–26       | 1.41*                      | –1.83**                  | –1.97**                  | 0.44                     | –0.22                    | –0.15                    |
| 0–39       | 1.72                       | –3.38                    | –1.95                    | –0.16                    | 1.74                     | 1.93                     |
| 0–52       | –0.64                      | 4.83***                  | 0.72                     | –0.46                    | 1.38                     | 1.51                     |
| <i>ITT</i> |                            |                          |                          |                          |                          |                          |
| 0          | 1.84***                    | –                        | –                        | 0.85**                   | –                        | –                        |
| 0–1        | 0.06                       | –1.39**                  | –0.36                    | –0.71*                   | 0.53                     | 0.22                     |
| 0–3        | 0.34                       | –2.15***                 | –0.43                    | –0.01                    | –0.04                    | 0.73                     |
| 0–6        | –0.28                      | 1.67                     | –0.03                    | –0.78                    | –0.63                    | 1.45**                   |
| 0–12       | 1.56                       | 0.73                     | –1.03                    | 0.38                     | 0.77                     | 4.61                     |
| 0–26       | 1.38*                      | –0.57                    | –1.22                    | 1.09                     | –0.42                    | 0.02                     |
| 0–39       | –0.74                      | –0.15                    | 0.60                     | –0.33                    | 2.11                     | 2.21                     |
| 0–52       | –2.83                      | 1.48                     | 1.02                     | –3.91                    | 3.26                     | 2.54                     |

Notes: CRP = C-reactive protein (mg/L); ami = amisulpride; ari = aripiprazole; olan = olanzapine. G1: Previous antipsychotic treated patients; G2: Antipsychotic naïve patients; <sup>0</sup> = *b*<sub>0</sub> intercept level: male patients with amisulpride, mean time on the chosen medication (centered), mean BMI (centered), and in the absence of drug use and smoking; <sup>a</sup> = aripiprazole versus amisulpride (reference medication); <sup>b</sup> = olanzapine versus amisulpride (reference medication); *b* = regression weights.

The results for the covariate variables are not in focus but just adjustment factors and therefore not shown in the table.

\* *p* < 0.05.  
\*\* *p* < 0.01.  
\*\*\* *p* < 0.001.

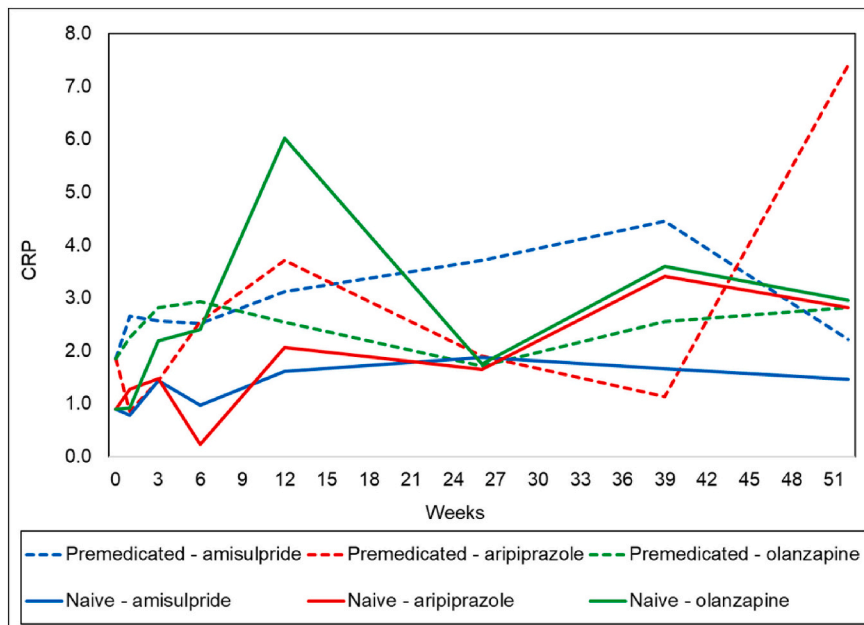
increased CRP levels. The Clinical Antipsychotic Trials of Intervention Effectiveness Study (CATIE) in chronic phase schizophrenia, showed that a 3 month treatment with olanzapine or quetiapine induced a significant increase in CRP levels (Meyer et al., 2009). A 12-month follow-up study in first episode psychosis (FEP), showed a significant increase

in CRP levels, weight gain, and increase in waist circumference. Almost 90% used olanzapine, risperidone, quetiapine, aripiprazole, sertindole and ziprasidone at baseline (Keinanen et al., 2018). A cross-sectional study of AP medicated schizophrenia patients on olanzapine, quetiapine, clozapine or risperidone found significantly higher levels of CRP and IL-6 compared to a non-medicated group of patients (Gurung et al., 2018).

Our study adds to these previous finding by confirming an initial CRP reduction in the first 3 weeks of aripiprazole use, as well extending this by demonstrating similar effects after 26 weeks for aripiprazole users previously exposed to AP, followed by an increase at the end of follow-up. While interpretation of this pattern remains speculative, it could include factors, such as an anti-inflammatory effect by aripiprazole or contrasting effects of the drug in different phases of the illness.

The mechanisms by which AP affect inflammatory pathways remain unknown. Several studies have shown alterations in the levels of cytokines following AP use, in both pro- and anti-inflammatory directions in FEP patients and during acute psychotic episodes in individuals with chronic schizophrenia (de Witte et al., 2014; Juncal-Ruiz et al., 2018; Miller et al., 2011; Tourjman et al., 2013). Sobis et al. (2015) reported a reduction of several pro-inflammatory cytokines such as IL-6, tumor necrosis factor-alpha (TNF-α), IL-1β, interferon gamma (IFN-γ), IL-12 and IL-23, and anti-inflammatory cytokines IL-4 and transforming growth factor β1 (TGF-β1) together with marked increased level of IL-10 after 4 weeks of aripiprazole treatment, which supports a predominantly anti-inflammatory effect by this drug.

Furthermore, the association between higher baseline BMI and higher baseline CRP levels is in line with findings from other studies. Higher BMI has been shown to be correlated with higher CRP levels in the general population (Choi et al., 2013). In a study of 106 patients with schizophrenia, BMI was positively correlated with CRP levels, but was independent of age, sex, race, education and cotinine, a nicotine metabolite levels (Boozalis et al., 2018). Furthermore, CRP was negatively correlated with high-density lipoproteins (HDL) in the total sample and in overweight/obese patients, but not in patients with normal weight. The authors of this study concluded that overweight/obesity is associated with increased inflammation and dyslipidemia in patients with schizophrenia (Boozalis et al., 2018). An indirect effect of aripiprazole via its lower propensity to induce metabolic changes than olanzapine and the other first-line NGAP might also have contributed to the CRP reduction we have found in the initial weeks of follow-up.



**Fig. 3.** Estimated changes in CRP levels, comparing aripiprazole and olanzapine with amisulpride per protocol—previously medicated and medication naïve groups. CRP = C-reactive protein (mg/L). Premedicated: Previously exposed to antipsychotics prior to inclusion. Naïve: Antipsychotic-naïve without any antipsychotics exposure prior to inclusion. Amisulpride is the reference antipsychotic medication. The estimates are adjusted for time on first medication, gender, body mass index (BMI) and clinical drug use scale (CDUS).

Our findings are consistent with other studies, insofar as they confirm differences between AP regarding effects on the immune system, yet the role of the influence of possible mediating effects of metabolic changes induced by different AP needs to be elucidated in further studies.

### 5.1. Strengths and limitations

The main strengths of the present study are its pragmatic design, reflecting everyday clinical practice, as well as the long follow-up. The inclusion of 39% AP-naïve patients and the random assignment to three different NGAP with diverse receptor and side effect profiles are additional strong points. The one-year follow-up allowed an investigation of the long-term effects of the three AP on CRP levels. A limitation is the substantial drop out rate of about 46% and some missing biological data. We cannot rule out the possibility that this could have influenced the results, but if so, the direction of any such influence is hard to predict. However, as reported in a previous publication of the trial's primary outcomes – change of the PANSS total score - sensitivity analyses of missingness supported missingness to be at random (Johnsen et al., 2020). Another limitation of this study was the lack of white blood cell count, which could have contributed to the identification of potential infectious conditions, as well as lack of other inflammatory markers. However, high sensitivity CRP is considered to be a robust and predictive inflammatory marker with well-established cut-off.

### 5.2. Conclusion

Treatment with amisulpride, aripiprazole and olanzapine showed different effects on CRP levels in patients with SSD, modified by previous AP exposure status. This finding suggests that antipsychotic drugs may vary with respect to their influence on pro-inflammatory pathways.

### Ethical standards

The study was approved by the Regional Committees for Medical and Health Research Ethics 2010/3387, and the Norwegian Medicines Agency in Norway (11/01070), and the Etikkommission der Medizinische Universität Innsbruck, together with the Federal Office for Safety in Health Care (BASG) in Austria. The authors assert that all procedures

complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

### Financial support

The BeSt InTro study was funded by the Research Council of Norway (grant numbers #213727 and #223273), the Western Norway Regional Health Authority (grant numbers #911820 and #911679), and the participating hospitals and universities.

Protocol code number: BergenPsychosisProject2. EudraCT number 2010-022307-22.

ClinicalTrials.gov identifier: NCT01446328.

The funding sources played no role in the study design, or in the collection, analysis and interpretation of the data.

### Declaration of competing interest

The authors report no conflicts of interest related to the present study.

### Acknowledgements

The authors thank all the participants for contributing to this study, the staff of the Research Department, Division of Psychiatry, Haukeland University Hospital (HUH), Stavanger University Hospital, St Olav's University Hospital, and the Medical University of Innsbruck in Austria. We also thank the Division of Psychiatry, HUH for financial support, the clinical departments for their cooperation, and the Stiftelsen Kristian Gerhard Jebsen (SKGJ) in Norway for their support.

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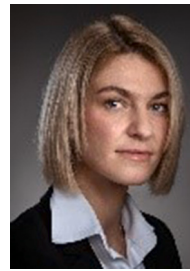
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