Hostility and aggressive behaviour in first episode psychosis: results from the OPTiMiSE trial

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Abstract: Aim: The aim of this paper is to determine clinical factors related to hostility and disturbing and aggressive behaviour and to examine the effect of medication on these behaviours in FEP. Methods: Data from phase I and II of the OPTiMiSE trial are used. Outcome measures are the hostility item of the Positive and Negative Syndrome Scale (PANSS P7) and the disturbing and aggressive behaviour domain of the Personal and Social Performance scale (PSP-D). Results: Moderate, severe or extreme hostility (PANSS P7 $>$ 3) was present in 42 patients (9.4%). The PANSS P7 and PSP-D were low to moderate but significantly associated with the selected PANSS items: delusions, hallucinatory behaviour, excitement, tension, uncooperativeness, unusual thought content, impulsivity, and lack of judgement and insight. In a subsample of 185 patients (41.5%) with baseline PANSS P7 $>$ 1, the PANSS P7 and PSP-D scores improved in the first 4 weeks of amisulpride treatment. This effect remained significant after controlling for baseline positive symptoms (PANSS P1-P6). No significant differences were found between olanzapine and amisulpride in the second phase of the trial. Conclusion: Clinical risk factors such as poor impulse control, uncooperativeness and excitement could help clinicians in detecting and treating hostile and aggressive behaviour in FEP. Amisulpride could be an effective antipsychotic choice in the treatment of FEP patients who express hostile or aggressive behaviour. Future research is needed to compare the effects of amisulpride and olanzapine on hostility in FEP during the first weeks of treatment.

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Hostility and aggressive behaviour in first episode psychosis: Results from the OPTiMiSE trial

Margo D.M. Faay [a,*], G. Caroline M. van Baal [b], Celso Arango [c], Covadonga M. Díaz-Caneja [c], Gregor Berger [d], Stefan Leucht [e], Julio Bobes [f], Pilar A. Sáiz [f], María Paz García-Portilla [f], Resy van de Brug [a], Jocelyn Petter [a], Inge Winter-van Rossum [a], Iris E. Sommer [g,h]

[a] Department of Psychiatry, University Medical Center Utrecht, Utrecht, the Netherlands
[b] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands
[c] Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), CIBERSAM, School of Medicine, Universidad Complutense, Madrid, Spain
[d] University Hospital of Psychiatry Zurich, Department of Child and Adolescent Psychiatry and Psychotherapy, Zurich, Switzerland
[e] Department of Psychiatry and Psychotherapy, Technical University Munich, Munich, Germany.
[f] Department of Medicine-Psychiatry, University of Oviedo, Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), INEUROPA, CIBERSAM, Oviedo, Spain
[g] Department of Neuroscience, University Medical Center Groningen, Deusinglaan 2, Groningen, the Netherlands
[h] Department of Medical and Biological Psychology, University of Bergen, Norway

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ABSTRACT

Aim: The aim of this paper is to determine clinical factors related to hostility and disturbing and aggressive behaviour and to examine the effect of medication on these behaviours in FEP.
Methods: Data from phase I and II of the OPTiMiSE trial are used. Outcome measures are the hostility item of the Positive and Negative Syndrome Scale (PANSS P7) and the disturbing and aggressive behaviour domain of the Personal and Social Performance scale (PSP-D).
Results: Moderate, severe or extreme hostility (PANSS P7 > 3) was present in 42 patients (9.4%). The PANSS P7 and PSP-D were low to moderate but significantly associated with the selected PANSS items: delusions, hallucinatory behaviour, excitement, tension, uncooperativeness, unusual thought content, impulsivity, and lack of judgement and insight. In a subsample of 185 patients (41.5%) with baseline PANSS P7 > 1, the PANSS P7 and PSP-D scores improved in the first 4 weeks of amisulpride treatment. This effect remained significant after controlling for baseline positive symptoms (PANSS P1-P6). No significant differences were found between olanzapine and amisulpride in the second phase of the trial.
Conclusion: Clinical risk factors such as poor impulse control, uncooperativeness and excitement could help clinicians in detecting and treating hostile and aggressive behaviour in FEP. Amisulpride could be an effective antipsychotic choice in the treatment of FEP patients who express hostile or aggressive behaviour. Future research is needed to compare the effects of amisulpride and olanzapine on hostility in FEP during the first weeks of treatment.

1. Introduction

A considerable proportion of patients with first episode psychosis (FEP) are involved in aggressive incidents. Studies estimate that around 30% of patients commit at least one violent act during their first psychotic episode (Large and Nielssen, 2011; Winsper et al., 2013). Aggression often leads to a number of negative consequences for the patients as well as their immediate social network, health care workers and the public, such as prolonged hospitalisation or social isolation (Lahera et al., 2015; Volavka, 2008).

For clinicians, it is essential to have some knowledge of the factors that are associated with hostile or aggressive behaviour, as this enables risk assessment and treatment planning. Clinical risk factors for hostile or aggressive behaviour in psychotic disorders in general include previous violence, symptoms of mania, substance abuse, treatment non adherence, excitement, impulsivity, lack of insight and positive symptoms (Arango, 2000; Arango et al., 1999; Bobes et al., 2009; Faay and van Os, 2020; Fazel et al., 2009; Volavka et al., 2016; Witt et al., 2013). Specifically for FEP, a meta-analysis identified risk factors for any type of violence, which included younger age, male sex, substance

* Corresponding author at: UMC Utrecht, internal post no A01.126. Heidelberglaan 100, P.O. Box 85500, 3508 GA Utrecht, the Netherlands.
E-mail address: m.d.m.faay@umcutrecht.nl (M.D.M. Faay).

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abuse, manic symptoms, lower level of education and longer duration of untreated psychosis (Large and Nielssen, 2011). While positive symptoms are a risk factor for aggressive behaviour in more chronic psychotic disorders, the findings within FEP populations are inconsistent. In contrast to meta-analytic data (Large and Nielssen, 2011), a 10-year follow-up study of FEP found higher positive symptom scores in patients with violent behaviour (Langeveld et al., 2014). More specifically, certain positive symptoms, such as delusions and uncommon beliefs were associated with violence in FEP (Coid et al., 2013) but a recent study in an ultra-high-risk sample found no significant relation between delusions, unusual thought content, hallucinations and violent behaviour (Brucato et al., 2019). Next to positive symptoms, clinical risk factors that are observed from patients' behaviour could be important for risk management. Impulsivity is associated with violent behaviour in early psychosis (Moulin et al., 2018a, 2018b). In patients with more chronic psychotic disorders, uncooperativeness and excitement were related to hostile and aggressive behaviour next to impulsiveness (Faay and van Os, 2020). However, as far as we are aware, there are no studies examining the association between symptoms such as uncooperativeness, excitement and tension with aggressive behaviour in FEP.

Although violence, aggression and hostility are different, hostile behaviour can be seen as a risk factor for violent or aggressive acts since this behaviour is often observed prior to incidents (Large and Nielssen, 2011; Witt et al., 2013). Moreover, since most major studies do not include a separate measure of violence or aggression, the hostility item of the Positive and Negative Syndrome Scale (PANSS P7 (Kay et al., 1987)) is often used as a proxy to give an indication of the level of aggressive behaviour.

Some randomized trials presented post-hoc analysis of the PANSS hostility item. The European First Episode Schizophrenia Trial (EUFEST) compared five antipsychotic drugs in 498 patients with first episode schizophrenia, schizoaffective disorder or schizophreniform disorder in terms of efficacy and tolerability. In a subset of 302 patients with at least minimal hostility (>1) at baseline, olanzapine was superior to other antipsychotics in reducing hostility (Volavka et al., 2011). A similar result was found in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study including 1493 patients with schizophrenia. Post-hoc analyses of this study found olanzapine to be significantly superior in reducing hostility compared with perphenazine, quetiapine, ziprasidone and risperidone (Volavka et al., 2014). A recent meta-analysis, including these trials, compared the effect of antipsychotics on hostility in 18 randomized studies. A small but significant effect was found for second-generation as compared to first-generation antipsychotics (Faay et al., 2018). Especially clozapine was superior, in line with previous studies (Frogley et al., 2012; Glazer and Dickson, 1998; Spivak et al., 1997). Current clinical guidelines recommend clozapine for patients who do not respond to two adequate trials with different antipsychotics (Warnez and Alessi-Severini, 2014). Thus, FEP patients can only start with clozapine after several weeks of treatment. Evidence considering the effectiveness of other second-generation antipsychotics on hostile and aggressive behaviour in the first weeks of treatment is therefore needed.

The present paper focuses on the PANSS P7 hostility item and the PSP-D disturbing and aggressive behaviour domain in the Optimization of Treatment and Management of Schizophrenia in Europe (OPTiMiSE) trial. We aim to determine clinical factors related to hostility and disturbing and aggressive behaviour, and to examine the effect of medication on these behaviours in FEP patients. To examine the effect of medication, there is a two-fold aim: 1) to describe the short-term effect of amisulpride on hostility and disturbing and aggressive behaviour and 2) to compare the effect of continuation of amisulpride versus switching to olanzapine on hostility and disturbing and aggressive behaviour in patients who were not in remission after four weeks of treatment with amisulpride.

2. Methods

2.1. OPTiMiSE trial

The rationale and design of the OPTiMiSE trial is described elsewhere (Leucht et al., 2015). A total of 481 patients with first episode schizophrenia, schizophreniform or schizoaffective disorder were included in 27 sites across European countries and Israel. In phase I, patients received open label amisulpride (200–800 mg/d). Patients who were not in remission after 4 weeks continued in phase II of the trial and were randomized to 6 weeks double blind treatment with either a continuation of amisulpride or a switch to olanzapine (5–20 mg/d). If these patients still not reached remission criteria at week 10, they entered phase III where they received 12-weeks open label clozapine (100–900 mg/d). Dosing was flexible in all three phases of the trial. For the current analysis, data from phase I and II are used. Each country obtained regulatory approval. All participants provided written informed consent. A data safety monitoring board oversaw the study.

2.2. Measures

The Positive And Negative Syndrome Scale (PANSS (Kay et al., 1987)), was used to assess the severity of clinical symptoms associated with psychosis. All 30 PANSS items are scored from absent (1) to severe impairment (7), resulting in a total score between 30 and 210. The primary outcome measure for the current analysis is the P7 hostility item, an item on the positive subscale. Hostility is defined as "verbal and non-verbal expressions of anger and resentment, including sarcasm, passive-aggressive behaviour, verbal abuse and assaultiveness" (Kay et al., 1987). The score is based on interpersonal behaviour during the interview and reports by primary care workers or family during the past week. A score of 1 indicates absent hostility, a score of 2 indicates minimal presence of hostility ("questionable pathology"), 3 is labelled as "mild", 4 is "moderate", 5 indicates "moderate-severe", 6 is "severe" and a score of 7 indicates "extreme", including marked anger, resulting in physical assault towards others.

Next to the PANSS, the Personal and Social Performance Scale (PSP (Morosini et al., 2000) was used. The PSP consists of four main domains of functioning: A) social useful activities, B) personal and social relationships, C) self-care and D) disturbing and aggressive behaviour. All domains are scored on a 6-point scale which has a specific description of the degrees of severity for the "disturbing and aggressive behavior" domain. This domain is based on behaviour during the past month and scored from absent (1) to very severe (6), indicating "frequent aggressive acts, aimed at, or likely to cause severe injuries".

For the analysis of clinical factors associated with hostility, we selected seven PANSS items to see if these are related to PANSS P7 and PSP-D. We included the four PANSS items that are in the Excitement Component (PANSS-EC), along with hostility: P4 excitement, G4 tension, G8 uncooperativeness and G14 poor impulse control (Montoya et al., 2011). Impulsivity was associated with violence in FEP (Moulin et al., 2018b) and more chronic populations (Faay and van Os, 2020), but for excitement, tension and uncooperativeness, there is lacking evidence in a population of FEP. Next to these items, we wanted to examine whether delusions and hallucinations are associated with hostility or aggression because of the contrasting results from previous studies (Brucato et al., 2019; Coid et al., 2013; Langeveld et al., 2014; Large and Nielssen, 2011). We therefore included P1 delusions, P3 hallucinatory behaviour, and G9 unusual thought content, as this last item is associated with the first two.

Other measures used to describe the current sample include demographic data, type of care, duration of current psychosis, use of antipsychotics before inclusion to the trial and Clinical Global Impression (CGI (Guy, 1976)). Diagnosis was measured with the Mini International Neuropsychiatric Interview Plus (M.I.N.I. Plus (Sheehan et al., 1998)). All questionnaires and assessments were conducted by members of the

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local study team who were trained in the procedures and questionnaires. For administration of the PANSS, a standardised training was developed that included examination.

2.3. Statistical procedures

2.3.1. Clinical factors

To assess the clinical factors related to hostility (PANSS P7) and disturbing and aggressive behaviour (PSP-D) in a cross-sectional fashion, baseline values from the intention-to-treat sample were used to calculate Spearman's rank-order correlation (r_s). In general, correlation coefficients of 0.00 to 0.30 are considered negligible, 0.30 to 0.50 low, 0.50 to 0.70 moderate and >0.70 high to very high (Hinkle et al., 1988). This is, however, dependent of the context. For example, a correlation of >0.70 should be expected for instruments while correlations of a psychosocial nature rarely exceed 0.50 (Polit and Lake, 2010).

2.3.2. Phase I

In line with the hostility analysis of the CATIE and EUFEST studies, a subset of patients with a baseline PANSS P7 hostility score of at least 2 is used (i.e. PANSS P7 > 1), since there is no improvement possible in patients without baseline hostility.

For phase I, raw data were visualized using histograms, and mean values and *SD* of differences between baseline values of PANSS-P7/PSP-D and values at weeks 1, 2 and 4 were summarized in tables. These differences with their 95% Confidence Intervals (*CI*) were also visualized in high-low plots.

A general linear mixed model analysis was performed to test the differences in scores on PANSS-hostility at week 1, 2 and 4 (main effect and interaction with visit). Analyses were controlled for baseline phase I hostility, baseline phase I PANSS positive items P1-P6 (without hostility), and visit. Similar analyses were performed for PSP-D. General linear mixed models were chosen because these incorporate all available measurements and can handle missing values, assuming that these are missing at random.

2.3.3. Phase II

For the second phase, a new selection was made based upon hostility scores at the baseline phase II visit in week 4. For phase II, ITT analyses were performed. For both randomized groups, data were visualized using high-low plots, and mean values and *SD* of differences between baseline values of PANSS-P7/PSP-D and values at weeks 6, 8 and 10 were summarized in tables.

Again, general linear mixed models were used to test the effect of randomized treatment (continuation of amisulpride vs. switching to olanzapine) on PANSS-P7/PSP-D values at week 6, 8 and 10 (main effect and interaction with visit), controlling for baseline phase II hostility, baseline phase II PANSS positive items P1-P6 (without hostility) and visit. SPSS version 25 was used for all analyses.

3. Results

3.1. Sample characteristics

A total of 446 patients comprised the intention-to-treat sample. Baseline characteristics of this sample are described elsewhere (Kahn et al., 2018). From these 446 patients, 185 (41.5%) had a baseline PANSS hostility score > 1 and were included in the hostility subsample. Of this subsample, most patients had minimal (35.1%) or mild (42.2%) hostility. A total of 210 patients (47%) of the intention-to-treat sample scored on the PSP-D at baseline. Manifest, marked, severe or very severe disturbing or aggressive behaviour was present in 90 (20.2%) patients. 127 patients (28.5%) had both a hostility and PSP-D score. 178 patients (39.9%) scored on neither of these scales. 58 patients (13%) of the intention-to-treat sample had a hostility score but no PSP-D. Baseline characteristics of the hostility subsample are found in Table 1.

Table 1
Baseline characteristics of patients with baseline PANSS P7 hostility >1.

	Phase 1 $n = 185$	Phase 2 AMI $n = 16$	Phase 2 OLA $n = 12$
	N (%)	N (%)	N (%)
Age, years (mean; SD)	25.2 (5.7)	25.5 (5.7)	23.0 (4.8)
Sex			
Women	65 (35.1%)	3 (18.8%)	1 (8.3%)
Men	120 (64.9%)	13 (81.3%)	11 (91.7%)
Race			
White	166 (89.7%)	16 (100%)	11 (91.7%)
Other	19 (10.3%)	0 (0%)	1 (8.3%)
Education years[a] (mean; SD)	12.1 (3.0)	12.9 (2.4)	10.9 (2.5)
Employment status			
Employment or student	74 (40%)	4 (25%)	4 (33.3%)
Unemployed	111 (60%)	12 (75%)	8 (66.7%)
Disease type[b]			
Schizophreniform disorder	76 (41.1%)	5 (31.3)	4 (33.3)
Schizoaffective disorder	12 (6.5%)	0 (0%)	1 (8.3%)
Schizophrenia	97 (52.4%)	11 (68.7%)	7 (58.3%)
Comorbid major depressive disorder	15 (8.6%)	1 (6.7%)	0 (0%)
Suicidality[c]	26 (14.9%)	1 (6.6%)	3 (25%)
Substance abuse or dependence in the past 12 months	40 (23%)	1 (6.7%)	5 (41.7%)
Type of care baseline			
Inpatient	114 (61.6%)	9 (56.3%)	4 (33.3%)
Outpatient	71 (38.4%)	7 (43.8%)	8 (66.7%)
Duration of current psychosis, months (mean; SD)	6.8 (0.47)	9.13 (7.8)	9.8 (7.5)
Antipsychotic naïve at baseline	81 (43.8%)	10 (62%)	9 (75%)
CGI severity (mean; SD)	5.7 (0.9)	5.4 (0.9)	5.7 (0.6)
Clinical scores (mean; SD)			
PANSS total	85.9 (17.8)	95.9 (20.8)	81.4 (10.6)
PANSS positive	23.1 (5.1)	25.2 (6.5)	23.0 (4.4)
PANSS negative	20.7 (6.9)	24.9 (8.1)	22.7 (7.0)
PANSS general	42.1 (9.4)	45.7 (11.0)	42.1 (9.6)
PANSS P7 hostility[d]			
2- Minimal	65 (35.1%)	4 (25%)	1 (8.3%)
3- Mild	78 (42.2%)	8 (50%)	5 (41.7%)
4- Moderate	27 (14.6%)	3 (18.8%)	3 (25%)
5- Moderate/severe	9 (4.9%)	0 (0%)	2 (16.7%)
6- Severe	3 (1.6%)	1 (6.3%)	1 (8.3%)
7- Extreme	3 (1.6%)	0 (0%)	0 (0%)
PSP-D			
1- Absent	58 (32%)	6 (42.9%)	2 (20%)
2- Mild	61 (33.7%)	7 (50%)	2 (20%)
3- Manifest	33 (18.2%)	0 (0%)	2 (20%)
4- Marked	17 (9.4%)	0 (0%)	2 (20%)
5- Severe	11 (6.1%)	1 (7.1%)	2 (20%)
6- Very severe	1 (0.6%)	0 (0%)	0 (0%)

Data based on sample of patients with baseline hostility >1. PANSS = Positive and Negative Syndrome Scale; CGI = Clinical Global Impression; PSP-D = Personal and Social Performance Scale domain D: disturbing and aggressive behaviour; AMI = amisulpride; OLA = olanzapine.

[a] Years in school from age 6 onwards.
[b] According to the Mini International Neuropsychiatric Interview 5 plus.
[c] Suicidality includes medium to high suicide risk.
[d] Patients with absent hostility at baseline are not included in the hostility subsample.

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3.2. Correlations of PANSS items with hostility (PANSS P7) and disturbing and aggressive behaviour (PSP-D)

In the intention-to-treat sample, PANSS P7 hostility and PSP-D disturbing and aggressive behaviour domain are moderate but significantly associated with each other ($r_s = 0.43$, $p < 0.0005$) and with all other selected PANSS items (Table 2). Hostility has the strongest associations with poor impulse control ($r_s = 0.51$, $p < 0.0005$), uncooperativeness ($r_s = 0.43$, $p < 0.0005$) and excitement ($r_s = 0.30$, $p < 0.0005$). Disturbing and aggressive behaviour is associated with poor impulse control ($r_s = 0.50$, $p < 0.0005$) and uncooperativeness ($r_s = 0.30$, $p < 0.0005$). Gender and duration of psychosis were not significantly correlated with hostility.

3.3. Phase I

The mean PANSS P7 hostility score at baseline for the 185 patients in the hostility subsample was 3.0 ($SD = 1.1$; Table 3), corresponding to mild hostility. At week 4, this was 1.8 ($SD = 1.1$) corresponding to minimal or absent hostility. Fig. 1 shows the distribution of the hostility scores during phase I. At the end of phase I, 10 patients had hostility scores >3. The mean change in hostility scores from baseline to week 4 is −1.3 ($SD = 1.3$). The mean PSP-D score at baseline is 2.3 ($SD = 1.2$) corresponding to mild or manifest disturbing and aggressive behaviour and decreased to 1.5 ($SD = 0.9$) corresponding to absent or mild disturbing and aggressive behaviour at week 4, a mean change of −0.8 ($SD = 1.2$). Fig. 2 displays the mean change for both hostility and PSP-D.

Primary analysis of phase I hostility controlled for baseline phase I hostility and baseline phase I PANSS Positive items P1-P6, showed a significant reduction over visits ($F = 4.111$, $p = 0.017$). Marginal means were 2.199 (95% $CI = 2.040$; 2.358) at week 1, 2.119 (95% $CI = 1.969$; 2.269) at week 2, and 1.933 (95% $CI = 1.787$; 2.079) at week 4.

3.4. Phase II

A total of 93 patients continued to the second, double blind phase of the trial. 28 (30.1%) patients had a PANSS P7 hostility score > 1 at the baseline phase II visit in week 4 and were included in the hostility subsample of phase II. Of these 28 patients, six had a hostility score < 2 at baseline phase I. 16 patients were randomized to continue with amisulpride and 12 switched to olanzapine. There are no major differences in baseline characteristics (Table 1). The mean hostility score at baseline phase II for patients with amisulpride was 3.1 ($SD = 1.0$; Table 4) and for olanzapine this was 3.8 ($SD = 1.1$). At week 10, this was 2.5 ($SD = 1.2$) for patients with amisulpride and 2.3 ($SD = 1.6$) for patients with olanzapine. The mean change in phase II was −0.7 ($SD = 0.8$) for patients with amisulpride versus −1.4 ($SD = 1.4$) for patients with olanzapine (Fig. 2).

Controlled for baseline phase II hostility and baseline phase II PANSS Positive items P1-P6, primary analysis of the phase II data showed a trend but no significant reduction in hostility over visits ($F = 2.605$, $p = 0.087$). No significant differences between treatment arms were found ($F = 1.164$, $p = 0.292$).

Table 2
Correlations of selected PANSS items with PANSS P7 hostility and PSP-D.

PANSS items	Baseline phase 1 $n = 446$	
	PANSS P7 hostility	PSP-D
	Spearman's rho	Spearman's rho
P1 delusions	0.23***	0.23***
P3 hallucinatory behaviour	0.13**	0.15**
P4 excitement	0.30***	0.27***
P7 hostility	1.0	0.43***
G4 tension	0.19***	0.11*
G8 uncooperativeness	0.43***	0.30***
G9 unusual thought content	0.10*	0.19***
G12 lack of judgement and insight	0.25***	0.22***
G14 poor impulse control	0.51***	0.50***

Based on the complete sample of the OPTiMiSE trial at baseline; PANSS = Positive and Negative Syndrome Scale; PSP-D = Personal and Social Performance Scale domain D: disturbing and aggressive behaviours.
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

Table 3
Phase I PANSS P7 hostility and PSP-D mean scores and mean difference scores for patients with baseline hostility >1.

	Baseline phase I	Week 1	Week 2	Week 4	Baseline to week 4
PANSS P7 hostility					
Mean (SD)	3.0 (1.1)	2.4 (1.2)	2.1 (1.2)	1.8 (1.1)	
Mean difference (SD)		−0.7 (1.2)	−0.3 (1.0)	−0.4 (1.0)	−1.3 (1.3)
PSP-D					
Mean (SD)	2.3 (1.2)	1.8 (1.1)		1.5 (0.9)	
Mean difference (SD)		−0.4 (0.9)		−0.4 (0.9)	−0.8 (1.2)

PANSS = Positive and Negative Syndrome Scale; PSP-D = Personal and Social Performance Scale domain D: disturbing and aggressive behaviour; data based on the subsample of patients with baseline hostility >1.

4. Discussion

The prevalence of moderate, severe and extreme hostility (9.4%) and manifest, marked, severe or very severe disturbing and aggressive behaviour (20.2%) in this sample of FEP patients is low. As patients participating in a randomized controlled trial (RCT) are considered a selected sample, this may not reflect the total population of FEP patients. We found PANSS P7 hostility and PSP-D disturbing and aggressive behaviour low to moderate but significantly associated with each other and with PANSS items delusions, hallucinatory behaviour, tension, unusual thought content and lack of judgement and insight. The strongest associations, although still moderate, for both hostility and disturbing and aggressive behaviour were with poor impulse control, uncooperativeness and excitement. In the first phase of the trial, amisulpride use was associated with a reduction in hostile and aggressive behaviour and this association was still significant after controlling for baseline PANSS positive symptoms. In the second phase of the trial, we could not demonstrate a difference between continuation of amisulpride and a switch to olanzapine.

The prevalence of hostile and aggressive behaviour is the current sample is lower compared with other studies. In the EUFEST sample, 60.1% of the patients reported baseline hostility >1 compared with 41.5% patients in the current OPTiMiSE sample. The mean hostility score at baseline in the EUFEST sample was 3.2 ($SD = 1.1$) versus 3.0 ($SD = 1.1$) in the OPTiMiSE sample. When comparing these results with rates of violent behaviour in FEP, it should be mentioned that a hostility score of 2 is a low threshold to label behaviour as hostile. PANSS hostility score of 2 indicates "minimal; may be at the upper extreme of normal limits" (Kay et al., 1987). Moderate, severe or extreme aggression (i.e. PANSS hostility >3) was present in only 42 patients (9.4%) of the intention-to-treat sample at baseline. This is still lower than meta-analytic data indicating that around 30% of FEP patients engage in any violence (Large and Nielssen, 2011; Winsper et al., 2013).

There were differences between PANSS and PSP-D scores as only 127 patients (28.5%) scored on both scales. It is expected that patients score on the PSP but not on the PANSS as the PSP is based on

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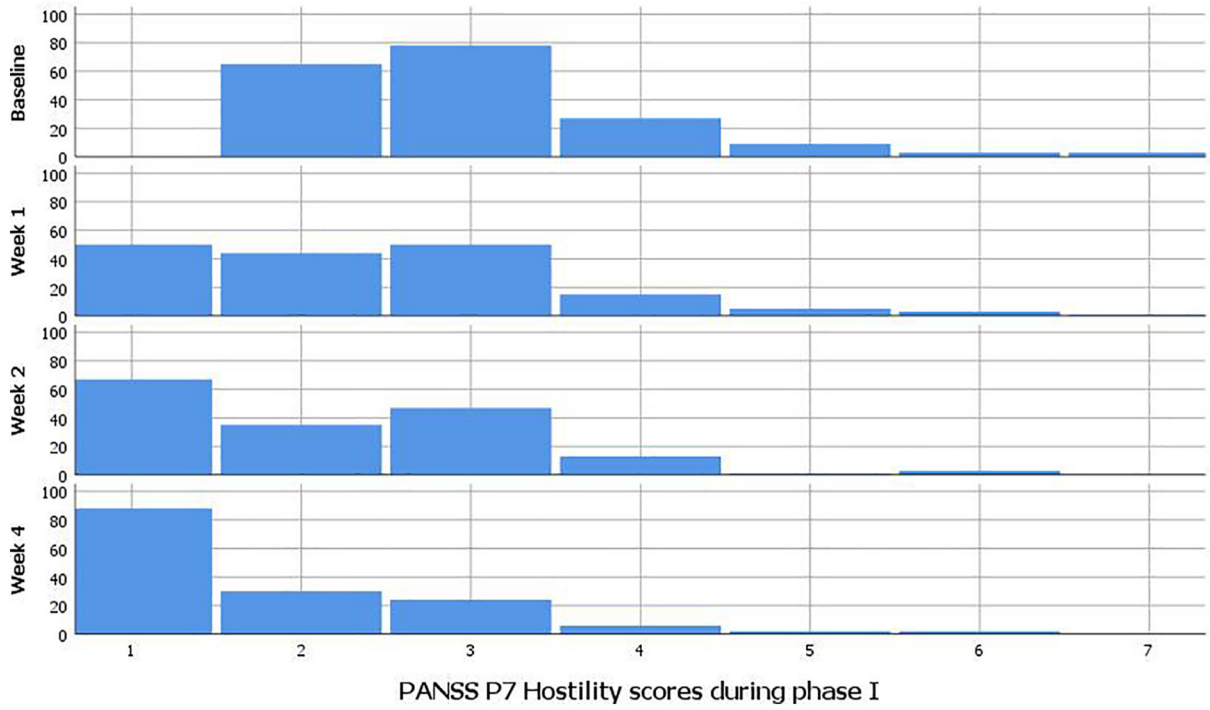

Fig. 1. Distribution of PANSS P7 hostility scores in patients with baseline hostility >1 during phase I. PANSS = Positive and Negative Syndrome Scale; frequencies of PANSS scores in phase I of the trial; based on the subsample of patients with baseline hostility >1.

behaviour during the past month and PANSS is aimed at behaviour during the past week. However, 32% of the hostility subsample did not score on the PSP-D at baseline. This could be because the PANSS is more sensitive than the PSP-D and questionable forms of hostility are not included on the latter.

The results from the correlational analysis are comparable with previous work. Combined analyses of the CATIE and EUFEST trials also found hostility associated with positive symptoms and lack of judgement and insight (Volavka et al., 2016). We confirmed the association for impulsivity and hostility with aggressive behaviour in

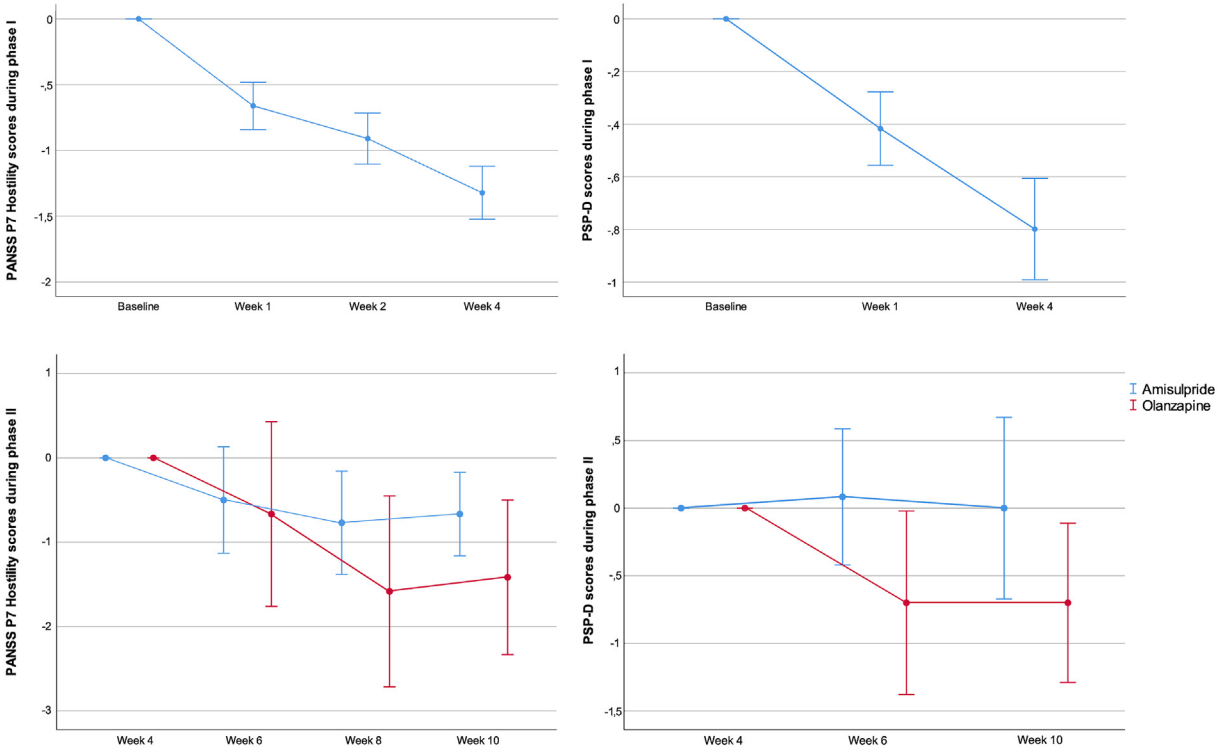

Fig. 2. Mean change of PANSS P7 hostility and PSP-D scores in patients with baseline hostility >1 during phase I and phase II. Data represent mean change and 95% CI for the change during phase 1 (amisulpride) and phase 2 (amisulpride or olanzapine); PANSS = Positive and Negative Syndrome Scale; PSP-D = Personal and Social Performance Scale domain D: disturbing and aggressive behaviour; based on the subsample of patients with baseline hostility >1.

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Table 4
Phase II PANSS P7 hostility and PSP-D mean scores and mean difference for patients with baseline phase II hostility >1: amisulpride versus olanzapine.

		Baseline phase II	Week 6	Week 8	Week 10	Baseline to week 10
PANSS P7 hostility	AMI, n = 16					
	Mean (SD)	3.1 (1.0)	2.6 (1.3)	2.4 (1.3)	2.5 (1.2)	
	Mean difference (SD)		−0.5 (1.1)	−0.4 (1.1)	0.1 (0.8)	−0.7 (0.8)
	OLA, n = 12					
	Mean (SD)	3.8 (1.1)	3.1 (1.8)	2.2 (1.5)	2.3 (1.6)	
	Mean difference (SD)		−0.7 (1.7)	−0.9 (1.1)	0.2 (1.3)	−1.4 (1.4)
PSP-D	AMI, *n* = 14					
	Mean (SD)	1.8 (1.1)	1.9 (1.2)		1.8 (1.3)	
	Mean difference (SD)		0.1 (0.8)		−0.1 (0.8)	0.0 (1.0)
	OLA, *n* = 10					
	Mean (SD)	3.0 (1.5)	2.1 (1.3)		2.2 (1.5)	
	Mean difference (SD)		−0.8 (1.0)		0.0 (0.5)	−0.7 (0.8)

PANSS = Positive and Negative Syndrome Scale; PSP-D = Personal and Social Performance Scale domain D: disturbing and aggressive behaviour; AMI = amisulpride, OLA = olanzapine; data based on the subsample of patients with baseline hostility >1.

FEP (Moulin et al., 2018a, 2018b). Additionally, we found excitement and uncooperativeness also associated with aggressive behaviour in a population of FEP. Meta-analytic data from psychotic disorders in general also found excitement associated with violence, but not uncooperativeness (Witt et al., 2013). More recent work found both excitement and uncooperativeness associated with different aggressiveness outcomes, although with differences between these measures (Faay and van Os, 2020). Compared with the different results considering the link between positive symptoms and violent behaviour in FEP (Brucato et al., 2019; Coid et al., 2013; Langeveld et al., 2014; Large and Nielssen, 2011) and psychotic disorders in general, where the positive symptom subscale is associated with violence (Volavka et al., 2016; Witt et al., 2013), we found hallucinations, delusions and unusual thought content low but significantly associated with hostility and disturbing and aggressive behaviour.

The reduction in hostility scores in phase I is in line with previous work. The mean reduction in hostility scores after one month for patients on amisulpride in the EUFEST study was around −1.2 (Volavka et al., 2011), which is comparable with our results at week 4 (−1.3). In both studies, the effect was still significant after controlling for other positive symptoms.

In the second phase of the trial, we could not find a significant difference in effect between amisulpride and olanzapine or a significant reduction over consecutive visits. This is likely due to the low sample size and a ceiling effect since the mean scores at baseline phase II are low and there can only be little improvement. In the EUFEST trial, olanzapine was significantly superior to amisulpride in reducing hostility during the first month of treatment ($P < 0.05$) (Volavka et al., 2011). The CATIE trial found olanzapine superior to other antipsychotics but did not use amisulpride (Volavka et al., 2014). A recent meta-analysis found that amisulpride and olanzapine reduce symptoms of schizophrenia to a similar degree (Huhn et al., 2019). Although the mechanisms of the effect of antipsychotics on aggression and hostility are still not fully understood, aggression is heterogeneous. Not all aggression from patients with psychotic disorders may be derived from psychosis. Therefore, efficacy on hostility may change among antipsychotics, not only because of the general effect of antipsychotics, but also because of differences in effect on sedation or other symptoms.

The current results have several implications for clinical practice. First, poor impulse control, excitement and uncooperativeness could be more important factors in violent behaviour than positive symptoms. This could help clinicians in observing and treating these kinds of behaviours. Second, these results contribute to the current understanding of the effect of antipsychotics on aggressive behaviour. Amisulpride is an effective agent in the treatment of hostile and aggressive patients and this effect is, at least partly, independent from baseline positive symptoms, but placebo-controlled studies are needed to confirm this effect. Moreover, while other studies are aimed at the long term effect of medications on hostility, the current results are focused on the effect in the first 10 weeks of treatment after the FEP, where patients are at particular risk for adverse behaviour, thus providing insight into the clinical factors and problems in these first weeks of treatment. We believe the current results imply that amisulpride should be considered for FEP patients with hostile or aggressive behaviour during the first weeks of treatment, specifically when olanzapine is contra-indicated because of the risk for weight-gain.

4.1. Limitations

The current study has several limitations. First, the OPTiMiSE trial was not designed for an analysis on hostile or aggressive behaviour. There will probably be some selection bias as patients were able to participate in a medication trial and sign an Informed Consent. Coercive treatment was an exclusion criterion and hostile patients may be more inclined to refuse study participation. The included patients are therefore likely to display less aggressive behaviour compared with FEP patients that are admitted to a hospital on an involuntary basis. Specifically in phase II, the sample size of the hostility subsample is low and this may have hampered the comparison between olanzapine and amisulpride. Second, by using two measures, we provide an indication of the level of aggressive and hostile behaviour but we do not have information on aggressive incidents. Incorporation of specific scales that measure aggression, such as incident report forms, is needed for a more objective measure of aggressive behaviour. Last, the PSP was not used according to its guidelines. The PSP is aimed at the behaviour in the past month but was assessed multiple times within one month, thus possibly losing subtle changes in patients' behaviour. Also, patients were selected based on their PANSS P7 hostility score and not on their PSP-D score.

4.2. Future research

Future research should address differential effects of different antipsychotic medication on hostility in FEP, in particular a comparison between olanzapine and amisulpride may be interesting in a sample of patients with more severe hostility scores. We hypothesize that amisulpride and olanzapine are equally effective against hostility during the first weeks of treatment and that a switch could be effective after a non-response for several weeks of treatment. This should ideally be studied with combined outcome measures such as PANSS P7 hostility and data from incidents reports. Moreover, research should focus on the effect of different dosages antipsychotics and the use of concomitant benzodiazepines on aggressive behaviour in FEP. For clinicians, these are interventions frequently used in order to prevent or treat aggressive behaviour. Although there is some evidence that higher dosages of antipsychotics are more effective (Faay et al., 2018; Fazel et al., 2014), many questions about these effects remain. For the effect of benzodiazepines on aggression or agitation in patients with psychosis there is little

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evidence (Baranchik et al., 2019; Zaman et al., 2018) and the decreased inhibition benzodiazepines cause might also increase impulsivity and dangerous behaviour (Guina and Merrill, 2018). As it is difficult to detangle cause from consequence, this should ideally be studied in a trial with fixed dosages and regulated benzodiazepine use.

5. Conclusions

The prevalence of moderate to severe hostility (9.4%) and disturbing and aggressive behaviour (20.2%) in this sample of FEP is low We found a significant reduction in PANSS hostility and PSP-D scores after 4 weeks of amisulpride which remained significant after controlling for baseline positive symptoms, thus indicating that amisulpride could be an effective antipsychotic choice in the treatment of FEP patients who express hostile or aggressive behaviour. Future research is needed to compare the effects of amisulpride and olanzapine on hostility in FEP during the first weeks of treatment.

Clinical risk factors such as delusions, hallucinatory behaviour, tension, unusual thought content and lack of judgement and insight could be important for risk assessment and treatment planning. But the most meaningful clinical risk factors in detecting and treating hostile and aggressive behaviour, are poor impulse control, uncooperativeness and excitement as these symptoms could be observed from patients' behaviour and thereby help clinicians in detecting and treating hostile and violent behaviour in FEP.

Contributors

SL, IWvR and IES designed the OPTiMiSE study. MDMF, CA, CMDC, GB, SL, JB, PAS, MPGP, RvdB, JP, IWvR and IES contributed to the data collection. MDMF and IES designed the current paper. MDMF and GCMvB undertook the statistical analysis. MDMF and IES wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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Declaration of competing interest

CA has been a consultant to or has received honoraria or grants from Acadia, Angelini, Gedeon Richter, Janssen Cilag, Lundbeck, Otsuka, Roche, Sage, Sanofi, Servier, Shire, Schering Plough, Sumitomo Dainippon Pharma, Sunovion and Takeda.

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JB has received research grants and served as consultant, advisor or speaker within de last 5 years for: AB-Biotics, Acadia Pharmaceuticals, Ambrosseti-Angelini, Casen Recordati, D&A Pharma, Exeltis, Gilead, Indivior, Janssen-Cilag, Lundbeck, Mundipharma, Otsuka, Pfizer, Roche, Sage Therapeutics, Servier, Schwabe Farma Ibérica, Shire, Takeda, research funding from the Spanish Ministry of Economy and Competiveness –Centro de Investigación Biomedica en Red area de Salud Mental (CIBERSAM) and Instituto de Salud Carlos III-, Spanish Ministry of Health, Social Services and Equality - Plan Nacional sobre Drogas- and the 7th Framework Program of the European Union.

PAS has been a consultant to and/or has received honoraria or grants from Adamed, CIBERSAM, European Comission, GlaxoSmithKline, Instituto de Salud Carlos III, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Plan Nacional Sobre Drogas and Servier.

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The remaining authors report no competing interests related to this work.

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