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The specific anti-hostility effect of lurasidone in patients with an acute exacerbation of schizophrenia: results of pooled post hoc analyses in adolescents and adults

Leslie Citrome[a], Elena Álvarez-Barón[b], Irene Gabarda-Inat[b], Karthinathan Thangavelu[c] and Michael Tocco[d]

Symptoms of hostility in patients during acute exacerbations of schizophrenia have been associated with aggressive behavior. Data suggest that some second-generation antipsychotics have specific anti-hostility effects, independent of sedation and positive symptom improvement. Two post hoc analyses were performed to examine the efficacy of lurasidone for reducing hostility in patients with schizophrenia. One analysis pooled adults ($N = 1168$) from 5 placebo-controlled, 6-week trials of lurasidone (40–160 mg). Another analysis pooled younger patients (up to age 25 years, $N = 427$) from the adult studies and a similarly designed trial of lurasidone (40 or 80 mg) in adolescent patients (13–17 years old). The outcome measure was mean change in the hostility item (P7) of the Positive and Negative Syndrome Scale (PANSS). To address pseudospecificity, results were adjusted for positive symptom change and sedation. In adults with a baseline PANSS hostility score ≥2, significant improvement in hostility was observed for all doses with a dose-related increase in effect size (Cohen's d): lurasidone 40 mg = 0.18, 80 mg = 0.24, 120 mg = 0.36, and 160 mg = 0.53. The same dose–response pattern was observed for the more severe hostility subgroups (P7: ≥3, ≥4), and in the early-onset population. Results suggest that lurasidone has specific, dose-related anti-hostility effects. *Int Clin Psychopharmacol* 40: 214–223

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[a]Department of Psychiatry and Behavioral Sciences, New York Medical College, Valhalla, New York, USA, [b]Angelini Pharma S.p.a, Global Medical Department, Rome, Italy, [c]Statistics Department, Medastats, LLC, Tampa and [d]Medical Department, Sumitomo Pharma America, Inc., Marlborough, Massachusetts, USA

Correspondence to Irene Gabarda Inat, Angelini Pharma España, S.L.U, Calle Antonio Machado, 78-80, Edificio Australia - 3a planta, 08840 Viladecans, Spain
Tel: +34 932534630; e-mail: irene.gabarda@angelinipharma.com

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Introduction

Hostility is a common symptom that complicates the clinical presentation of schizophrenia, occurring in at least one-third of both inpatients and outpatients (Bartels *et al*., 1991; Zhou *et al*., 2016; Knezevic *et al*., 2017). Hostility is included as an individual item (P7) in the positive symptom subscale of the Positive and Negative Syndrome Scale (PANSS; Kay *et al*., 2006). and has been identified by factor analysis as one of the four constituent items in the hostility/excitement factor (Marder *et al*., 1997; Lehoux *et al*., 2009; Wallwork *et al*., 2012). In a review of the anti-hostility effects of atypical antipsychotics the authors (Citrome and Volavka, 2021) note that "hostility differs conceptually from agitation, aggression, and violence" in that "hostility can be thought of as an underlying negative attitude toward situations and other people" and thus warrants analysis as an independent outcome. In individuals with schizophrenia, hostility has been associated with a stepwise increased risk of both aggressive and violent behavior (Swanson *et al*., 2006; Witt *et al*., 2013). Furthermore, hostility undermines the ability to develop and maintain a collaborative therapeutic alliance and has been identified as a significant risk factor for medication nonadherence/discontinuation which, in turn, is a significant predictor of relapse and rehospitalization (Lacro *et al*, 2002; de Haan *et al*., 2007; Novick *et al*., 2010; Czobor *et al*., 2013; Haddad *et al*., 2014; Volavka *et al*., 2016).

Atypical antipsychotics are an important treatment option for patients with schizophrenia who exhibit hostile or aggressive behavior, and the PANSS hostility item has been extensively analyzed as an outcome measure in antipsychotic treatment studies (Volavka *et al*., 1993, 2005, 2011, 2014, 2016; Czobor *et al*., 1995; Chengappa *et al*., 2003; Citrome *et al*., 2004, 2007, 2011, 2014, 2016a,b, 2019; Arango and Bernardo, 2005; Krakowski *et al*., 2006; Marder *et al*., 2007). With few exceptions involving clozapine and olanzapine, the majority of available anti-hostility efficacy data are based on post hoc analyses of randomized, double-blind, and placebo-controlled clinical trials.

Lurasidone is an atypical antipsychotic agent with high binding affinity for D_2, 5-HT_{2A}, and 5-HT_7 receptors

(antagonist); moderate affinity for 5-HT_{1A} receptors (partial agonist); and no appreciable affinity for H_1 and M_1 receptors (Ishibashi *et al.*, 2010). Lurasidone has demonstrated safety and efficacy in the treatment of schizophrenia in both short- and long-term studies (Meltzer *et al.*, 2011; Citrome *et al.*, 2012; Loebel *et al.*, 2013a, 2013b; Nasrallah *et al.*, 2013; Stahl *et al.*, 2013; Tandon *et al.*, 2016; Goldman *et al.*, 2017; Correll *et al.*, 2020). Moreover, the findings of two pairwise meta-analyses (PMAs) suggested that the approved doses of 40–160 mg/day are effective for overall symptoms of schizophrenia, as effective as most antipsychotics, well-tolerated, and less likely to cause weight gain or QTc prolongation (Huhn *et al.*, 2019; Pillinger *et al.*, 2020).

We summarize here post hoc analyses evaluating the anti-hostility efficacy of lurasidone in a pooled treatment sample of patients with schizophrenia, and a second sample with early-onset schizophrenia (i.e. younger patients ages 13–25 years) (Table 2b).

Methods

Adult patients

Individual patient data were extracted and pooled from five similarly designed randomized, double-blind, placebo-controlled, 6-week studies of lurasidone in adult patients (aged 18–75 years) with schizophrenia (Nakamura *et al.*, 2009; Meltzer *et al.*, 2011; Loebel *et al.*, 2013a; Nasrallah *et al.*, 2013; Ogasa *et al.*, 2013). Patients in these five studies had a diagnosis of schizophrenia based on Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) or the revised version of the fourth edition (DSM-IV-TR) (APA, 2000) with an acute exacerbation of psychotic symptoms as demonstrated by a Clinical Global Impression – Severity of Illness Scale (CGI-S) score of ≥4 (moderate or greater) and a PANSS total score ≥80 (moderate-to-severe). Key exclusion criteria were similar across all five studies, such as an acute or unstable medical condition; evidence of any other chronic disease of the central nervous system; alcohol or other drug abuse/dependence within the past 3–6 months; evidence of a severe, chronic movement disorder; or imminent risk of suicide (as judged by the study investigator).

Patients were randomized to receive placebo, or fixed-dose, once-daily, oral lurasidone (40, 80, 120, or 160 mg). Olanzapine (Meltzer *et al.*, 2011) and quetiapine XR (Loebel, *et al.*, 2013a) were used as active controls in one study each. Concomitant administration of lorazepam, temazepam, and zolpidem (for clinically significant anxiety/agitation, or insomnia), and anticholinergic agents or propranolol for movement disorders was permitted on an as-needed basis. Patients were hospitalized for the first 2–4 weeks of treatment and were then eligible for outpatient treatment, based on CGI-S scores and the clinical judgement of the investigator.

Early-onset (younger) patients

Individual patient data from the subgroup of patients with early-onset schizophrenia (criterion: onset between ages 13–25 years, inclusive) were extracted and pooled from the five adult studies noted above, and from a similarly designed study (Goldman *et al.*, 2017) in patients 13–17 years, inclusive; this latter study tested a lower fixed-dose of lurasidone (40 mg or 80 mg/d).

Each study was conducted in accordance with the Good Clinical Practices guidelines of the International Conference on Harmonization and with the ethical principles described in the Declaration of Helsinki. An independent Data and Safety Monitoring Board monitored each study. Prior to the conduct of any study procedures written informed consent was obtained from participants.

Efficacy in both the adult and early-onset patient groups was assessed using the PANSS total score, which was administered at baseline, day 3 or 4, day 7, and weekly thereafter up through week 6 endpoint.

Statistical analyses

The intent-to-treat (ITT) population consisted of all patients who were randomized and received at least one dose of study medication and had PANSS efficacy assessments at baseline and at least one postbaseline time point.

The PANSS hostility (P7) is rated on a 1–7 severity scale with 1 (absent), 2 (present but minimal), 3 (mild: indirect/restrained communication of anger, hostile expressions,

Table 1 Baseline characteristics of hostility severity subgroups in patients with schizophrenia

	P7 hostility ≥2	
(a) Adults	Lurasidone 40–160 mg (*N* = 792)	Placebo (*N* = 376)
Age, yrs, mean (SD)	38.0 (10.7)	38.1 (10.4)
Sex, male, *n* (%)	574 (72.5)	275 (73.1)
Race, *n* (%)		
White	346 (43.7)	154 (41.0)
Black	266 (33.6)	135 (35.9)
Asian	151 (19.1)	66 (17.6)
Other	29 (3.7)	21 (5.6)
PANSS, total score, mean (SD)	97.6 (11.2)	97.4 (12.0)
PANSS hostility item score, mean (SD)	3.1 (0.9)	3.1 (1.0)
(b) Early-onset, ages 13–25	Lurasidone 40–80 mg (*N* = 288)	Placebo (*N* = 139)
Age, yrs, mean (SD)	18.1 (3.8)	18.1 (4.0)
Sex, male, *n* (%)	205 (71.2)	93 (66.9)
Race, *n* (%)		
White	163 (56.6)	71 (51.1)
Black	52 (18.1)	35 (25.2)
Asian	45 (15.6)	21 (15.1)
Other	28 (9.7)	12 (8.6)
PANSS, total score, mean (SD)	97.1 (11.8)	96.1 (11.9)
PANSS hostility item score, mean (SD)	3.0 (1.0)	3.1 (0.9)

PANSS, Positive and Negative Syndrome Scale.

Table 2 Change from baseline to week 6 in the PANSS hostility item (P7; MMRM)

(a) Adults[a]

Subgroup: baseline PANSS hostility ≥2	Placebo $N=376$	Lurasidone 40 mg/d $N=224$	Comparison		Lurasidone 80 mg/d $N=255$	Comparison		Lurasidone 120 mg/d $N=215$	Comparison		Lurasidone 160 mg/d $N=98$	Comparison	
Week 6 change	LS mean change (SE)	LS mean change (SE)	Cohen's effect size	*P*-value	LS mean change (SE)	Cohen's effect size	*P*-value	LS mean change (SE)	Cohen's effect size	*P*-value	LS mean change (SE)	Cohen's effect size	*P*-value
PANSS hostility item, baseline ≥2	−0.63 (0.07)	−0.83 (0.09)	0.16	0.09	−0.95 (0.09)	0.26	0.005	−1.02 (−1.0)	0.34	<0.001	−1.31 (0.14)	0.57	<0.001
Additionally adjusted for PANSS-positive and somnolence	−0.59 (0.06)	−0.63 (0.08)	0.03	n.s.	−0.68 (0.08)	0.08	n.s.	−0.84 (0.09)	0.20	0.018	−0.94 (0.12)	0.29	0.007

Subgroup: baseline PANSS hostility ≥3	Placebo $N=260$	Lurasidone 40 mg/d $N=156$	Comparison		Lurasidone 80 mg/d $N=175$	Comparison		Lurasidone 120 mg/d $N=149$	Comparison		Lurasidone 160 mg/d $N=72$	Comparison	
Week 6 change	LS mean change (SE)	LS mean change (SE)	Cohen's effect size	*P*-value	LS mean change (SE)	Cohen's effect size	*P*-value	LS mean change (SE)	Cohen's effect size	*P*-value	LS mean change (SE)	Cohen's effect size	*P*-value
PANSS hostility item, baseline ≥3, unadjusted	−0.91 (0.09)	−1.12 (0.12)	0.17	n.s.	−1.30 (0.11)	0.34	0.004	−1.43 (0.12)	0.46	<0.001	−1.63 (0.17)	0.63	<0.001
Additionally adjusted for PANSS-positive and somnolence	−0.85 (0.08)	−0.89 (0.10)	0.03	n.s.	−0.98 (0.10)	0.12	n.s.	−1.17 (0.11)	0.28	0.011	−1.22 (0.14)	0.32	0.018

Subgroup: baseline PANSS hostility ≥4	Placebo $N=102$	Lurasidone 40 mg/d $N=54$	Comparison		Lurasidone 80 mg/d $N=72$	Comparison		Lurasidone 120 mg/d $N=58$	Comparison		Lurasidone 160 mg/d $N=29$	Comparison	
Week 6 change	LS mean change (SE)	LS mean change (SE)	Cohen's effect size	*P*-value	LS mean change (SE)	Cohen's effect size	*P*-value	LS mean change (SE)	Cohen's effect size	*P*-value	LS mean change (SE)	Cohen's effect size	*P*-value
PANSS hostility item, baseline ≥4, unadjusted	−1.34 (0.15)	−1.94 (0.22)	0.52	0.02	−2.13 (0.17)	0.68	<0.001	−2.12 (0.20)	0.67	<0.001	−2.52 (0.27)	1.03	<0.001
Additionally adjusted for PANSS-positive and somnolence	−1.40 (0.14)	−1.73 (0.18)	0.28	n.s.	−1.80 (0.15)	0.34	0.031	−1.76 (0.17)	0.31	0.079	−2.01 (0.22)	0.53	0.014

(b) Early-onset, ages 13–25[b]

Subgroup: baseline PAN0SS hostility ≥2	Placebo $N=139$	Lurasidone 40 mg/d $N=120$	Comparison		Lurasidone 80 mg/d $N=121$	Comparison		Lurasidone 120/160 mg/d $N=47$	Comparison	
Week 6 change	LS mean change (SE)	LS mean change (SE)	Cohen's effect size	*P*-value	LS mean change (SE)	Cohen's effect size	*P*-value	LS mean change (SE)	Cohen's effect size	*P*-value
PANSS hostility item, baseline ≥2, unadjusted	−0.40 (0.12)	−0.87 (0.13)	0.36	0.003	−1.18 (0.12)	0.59	<0.001	−1.19 (0.20)	0.65	<0.001
Adjusted for PANSS-positive and somnolence	−0.48 (0.11)	−0.70 (0.11)	0.17	n.s.	−1.02 (0.11)	0.41	<0.001	−0.83 (0.17)	0.26	0.065

Subgroup: baseline PANSS hostility ≥3	Placebo $N=98$	Lurasidone 40 mg/d $N=78$	Comparison		Lurasidone 80 mg/d $N=83$	Comparison		Lurasidone 120/160 mg/d $N=32$	Comparison	
Week 6 change	LS mean change (SE)	LS mean change (SE)	Cohen's effect size	*P*-value	LS mean change (SE)	Cohen's effect size	*P*-value	LS mean change (SE)	Cohen's effect size	*P*-value
PANSS hostility item, baseline ≥3, unadjusted	−0.89 (0.14)	−1.28 (0.16)	0.34	0.041	−1.64 (0.15)	0.62	<0.001	−1.76 (0.23)	0.75	0.001
Adjusted for PANSS-positive and somnolence	−0.95 (0.13)	−1.10 (0.14)	0.13	n.s.	−1.41 (0.13)	0.38	0.003	−1.36 (0.20)	0.35	0.07

(*Continued*)

Table 2 (*Continued*)

Subgroup: baseline PANSS hostility ≥4	Placebo *N* = 40	Lurasidone 40 mg/d *N* = 30	Comparison		Lurasidone 80 mg/d *N* = 38	Comparison		Lurasidone 120/160 mg/d *N* = 9	Comparison	
Week 6 change	LS mean change (SE)	LS mean change (SE)	Cohen's effect size	*P*-value	LS mean change (SE)	Cohen's effect size	*P*-value	LS mean change (SE)	Cohen's effect size	*P*-value
PANSS hostility item, baseline ≥4, unadjusted	−1.01 (0.26)	−1.34 (0.30)	0.23	n.s.	−2.01 (0.26)	0.74	0.005	−2.53 (0.52)	1.19	0.009
Adjusted for PANSS-positive and somnolence	−1.19 (0.23)	−1.21 (0.25)	0.10	n.s.	−1.78 (0.22)	0.44	0.038	−1.84 (0.42)	0.51	n.s.

The effect size (95% CI) was 0.18 (−0.03, 0.39). The 95% CI for effect size was based on the method described in Ialongo, (2016).
LS, least squares; MMRM, mixed-effects model for repeated-measures; n.s., not significant; PANSS, Positive and Negative Syndrome Scale; SE, standard error.
[a]All MMRM analyses for adults included study site and sex as covariates.
[b]All MMRM analyses for early-onset included study site and sex as covariates.

irritability), 4 (moderate: overtly hostile, showing frequent irritability and direct expressions of anger or resentment) to 7 (extreme).

The two pooled post hoc analysis groups (adult patients and early-onset patients) were analyzed separately. The adult and early-onset patient groups were subdivided into three groups based on the severity of PANSS hostility at baseline: PANSS hostility item score ≥2, ≥3, or ≥4. Change in the PANSS hostility item was evaluated using a mixed-effects model for repeated-measures (MMRM) including the baseline PANSS hostility (P7) item score as a covariate, and with treatment, study, visit, and treatment-by-visit interaction as fixed factors, assuming an unstructured covariance matrix. In a separate analysis, patient sex was included as a covariate in the MMRM model evaluating change in the PANSS hostility item score at week 6.

To evaluate the extent to which improvement in hostility was correlated with improvement in positive symptoms of schizophrenia, or with treatment-related somnolence effects, the analysis was conducted with and without adjusting for the modified PANSS-positive symptom factor score [calculated as a sum of the P1 (delusions), P3 (hallucinatory behavior), P5 (grandiosity), P6 (suspiciousness/persecution), N7 (stereotyped thinking), G1 (somatic concern), G9 (unusual thought content), G12 (lack of judgement and insight) items] as a time-varying covariate; a third analysis was performed that additionally adjusted for the presence/absence of treatment-emergent somnolence-related adverse events (defined as hypersomnia, hypersomnolence, sedation, or somnolence).

Statistical testing was performed at a two-sided significance level of 0.05 with no correction for multiplicity. This was a post hoc analysis and all results presented here are exploratory, with nominal *P*-values reported. Cohen's d effect sizes were calculated as the between-treatment group difference in LS mean change score divided by the model estimate of the pooled SD of the change scores. Ninety-five percent confidence intervals for Cohen's d were calculated based on Ialongo, (2016).

Results

Adults

A total of 1518 patients underwent baseline and post-baseline PANSS assessments and were included in the pooled ITT population, of whom 1168/1518 (76.9%) met the baseline PANSS hostility item score ≥2 and comprised the current analysis population. The proportion of patients with a baseline PANSS hostility item score ≥3 and ≥4 were 53.5 and 20.8%, respectively.

Baseline demographic and clinical characteristics were similar for lurasidone compared to placebo in each of the adult hostility subgroups (P7 item score ≥2, ≥3, or ≥4; Table 1a). The majority of patients were males in their 30 s or early

40 s; approximately 43% were white, 35% were black, and 22% were Asian or other races. Patients were experiencing moderate-to-severe levels of psychotic symptoms, with a mean PANSS total score of approximately 97.

The following concomitant medications were used by patients on an as-needed basis in the lurasidone and placebo groups, respectively: lorazepam, temazepam, or zolpidem (73.5 and 76.1%) or an anticholinergic agents or propranolol (27.5 and 17.0%). Patients who self-medicated with an antipsychotic medication were excluded from the analysis.

Early-onset (younger)

A total of 534 patients underwent baseline and post-baseline PANSS assessments and were included in the pooled ITT population, of whom 427/534 (80.0%) met the baseline PANSS hostility item score ≥2. The proportion of early-onset patients in the lurasidone and placebo groups with a baseline PANSS hostility item score ≥3 and ≥4 were 54.5 and 21.9%, respectively.

Baseline demographic and clinical characteristics were similar for lurasidone compared to placebo in each of the early-onset hostility subgroups (P7 item score ≥2, ≥3, or ≥4; Table 1b). The majority of patients were white males in the age range of 14–22 years. Patients were experiencing moderate-to-severe levels of psychotic symptoms, with a mean PANSS total score of approximately 97.

The following concomitant medications were used by patients on an as-needed basis in the lurasidone and placebo groups, respectively: lorazepam, temazepam, or zolpidem (38.9 and 39.6%) or an anticholinergic agents or propranolol (17.7 and 8.6%). Patients who self-medicated with an antipsychotic medication were excluded from the analysis.

Efficacy analyses

Adults: Hostility ≥2

In the adult population with a baseline PANSS hostility item score ≥2, significant improvement in mean change from baseline to week 6 in the PANSS hostility item score was observed during lurasidone treatment in MMRM analysis (Table 2a). The treatment effect of lurasidone on hostility exhibited a dose-dependent response, with the week 6 effect size (95% CI) increasing from low in the 40 mg [effect size, 0.18 (–0.03, 0.39)] and 80 mg [effect size, 0.24 (0.04, 0.44)] doses to moderate in the 120 mg [effect size, 0.36 (0.14, 0.58)] and 160 mg [effect size, 0.53 (0.27, 0.80)] doses (Fig. 1a). Combined adjustment for change in PANSS-positive symptoms and treatment-emergent somnolence reduced the effect of lurasidone on hostility, but the dose–response effect remained in evidence with significant effects at the 120 and 160 mg doses (Table 2a; Fig. 1a). A similar dose effect was observed for the time-to-onset of the anti-hostility treatment effect with the 120 and 160 mg doses of lurasidone demonstrating significant efficacy by week 1, the 80 mg dose by week 2, and the 40 mg dose by week 3 (Fig. 2a).

Adult: Hostility ≥3

In the adult population with a baseline hostility score ≥3, significant improvement in the hostility score was observed at week 6, with a dose–response effect, during lurasidone treatment with the 80 mg [effect size, 0.30 (0.06, 0.54)], 120 mg [0.47 (0.21, 0.73)], and 160 mg [0.58 (0.27, 0.89)] doses, but the lower [40 mg; effect size, 0.21 (–0.06, 0.47)] dose had no significant effect (Table 2a; Fig. 1a). For the higher (120–160 mg) doses, the treatment effect of lurasidone on hostility remained significant at week 6 for the subgroups with baseline hostility score ≥2 and ≥3 (but not ≥4) after combined adjustment for positive symptoms and somnolence, but effect sizes were reduced (Table 2a; Fig. 1a). A dose effect was also observed for the time-to-onset of the anti-hostility treatment effect with the 120 and 160 mg doses of lurasidone demonstrating significant efficacy by week 1, the 80 mg dose by week 2, and the 40 mg dose by week 3.

Adult: Hostility ≥4

In the adult population with a baseline hostility score ≥4, significant improvement in the hostility score was observed at week 6, with a similar effect size at the low doses [40 mg: effect size, 0.60 (0.13, 1.07); 80 mg: effect size, 0.57 (0.18, 0.97)], and larger effect sizes at the higher doses [120 mg: effect size, 0.72 (0.28, 1.16); 120 mg: effect size, 0.83 (0.33, 1.34)] (Table 2a; Fig. 1a). For the higher (120–160 mg) doses, the treatment effect of lurasidone on hostility remained significant at week 6 after combined adjustment for positive symptoms and somnolence, but effect sizes were reduced (Table 2a; Fig. 1a). In this more severe hostility subgroup, significant separation from placebo was observed by week 3; however, no dose effect was evident.

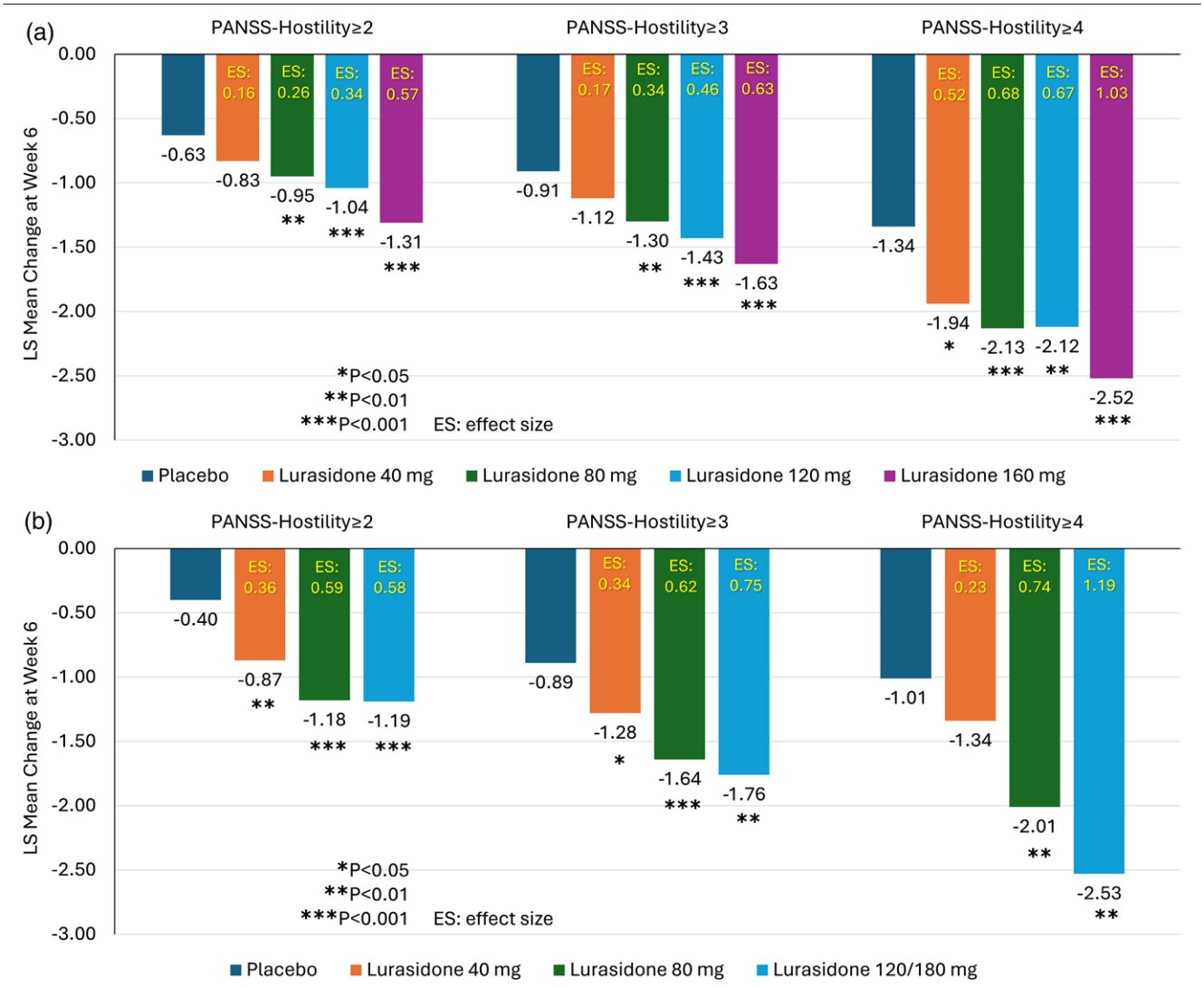
Adult: Lack of effect of somnolence on anti-hostility effect of lurasidone

Week 6 P7 hostility change scores were similar after adjustment for PANSS-positive symptoms and after adjustment for both PANSS-positive symptoms and somnolence, respectively, in the baseline hostility ≥2 group (placebo: –57, –59; lurasidone 40 mg: –61, –63; lurasidone 80 mg: –66, –68; lurasidone 120 mg: –82, –84; and lurasidone 160 mg: –92, –94). Adding somnolence as a covariate had similarly minimal effects on week 6 hostility change scores in the baseline hostility ≥3 and ≥4 groups.

Early-onset: Hostility ≥2

In the early-onset population with a baseline hostility score ≥2, significant improvement in the hostility score

Fig. 1



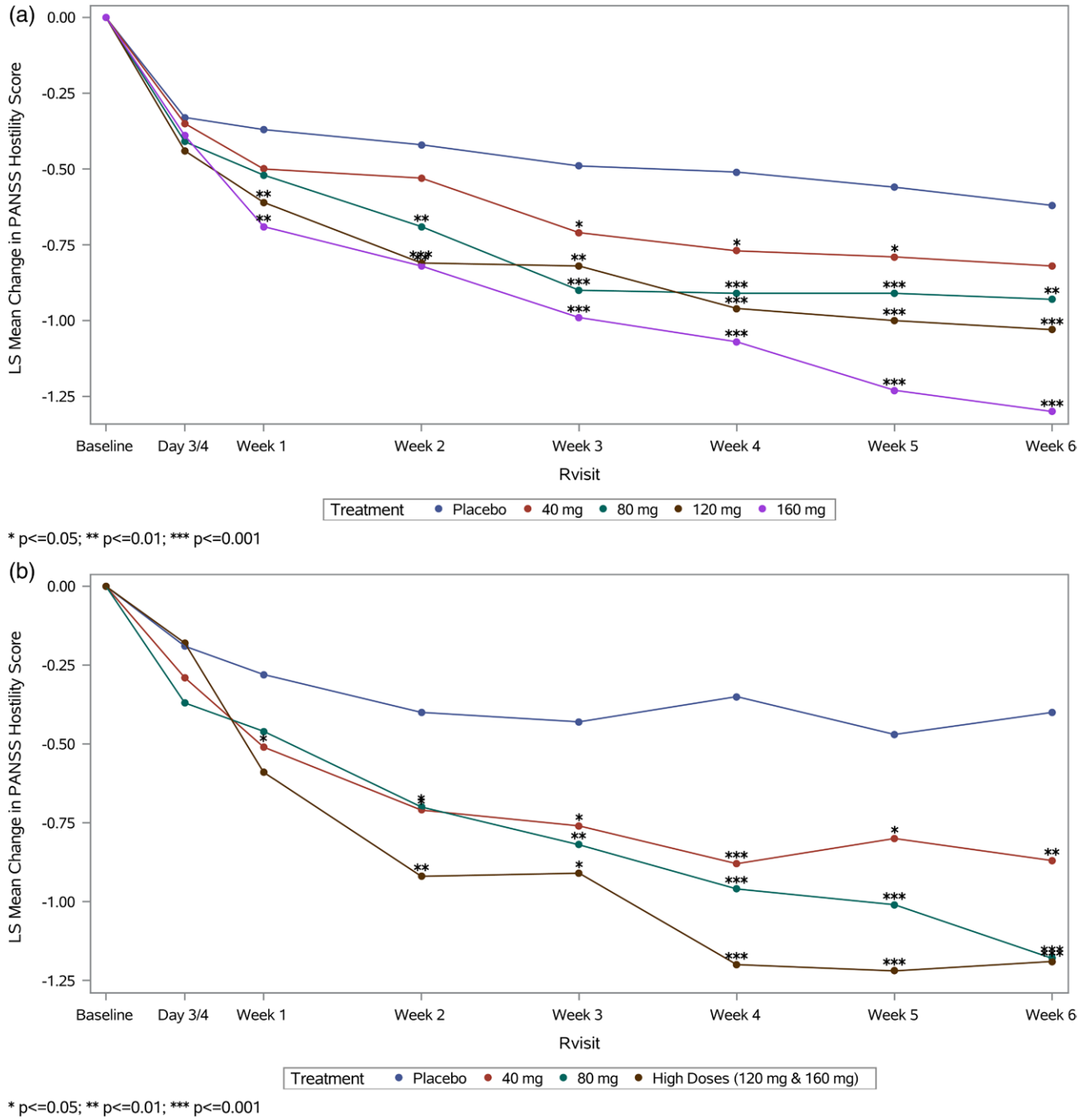
Change from baseline at week 6 in PANSS hostility score for lurasidone vs. placebo. (a) Adults (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. (b) Early-onset, ages 13–25 (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$). ES, effect size; PANSS, Positive and Negative Syndrome Scale.

was observed on lurasidone, with week 6 effect sizes increasing from the 40 mg [0.36 (0.08, 0.64)] and 80 mg [0.57 (0.29, 0.84)] doses to the higher 120/160 mg [0.65 [0.26, 1.04)] doses. For the higher doses (80 mg and combined 120/160 mg), the treatment effect of lurasidone remained significant at week 6 after adjustment for positive symptoms and somnolence, but effect sizes were reduced (Table 2b; Fig. 1b). Significant separation from placebo was observed at week 1 for the combined 120/160 mg doses and was evident at week 2 for the 40 and 80 mg doses.

Early-onset: Hostility ≥3 and ≥4

In the early-onset (younger) population with a baseline hostility score ≥3, significant improvement in the hostility score was observed on the higher doses of lurasidone, with week 6 effect sizes increasing from the 40 mg [nonsignificant, with effect size, 0.32 (−0.03, 0.67)] to significant for the 80 mg [0.58 (0.25, 0.91)] and 120/160 mg [0.76 (0.29, 1.23)] doses (Table 2b; Fig. 1b). A similar dose–response pattern was observed for the subgroup with a baseline hostility score ≥4; however, the sample sizes in this severity subgroup were small, especially for the combined 120/160 mg dose group (Table 2b; Fig. 1b). Finally, compared to adjustment for positive symptoms alone, combined adjustment for positive symptoms and somnolence had a similar magnitude of reduction in the effect size for the higher baseline severity subgroups (hostility score ≥2 and ≥3) as it had on the lower severity subgroup (hostility score ≥2) as shown in Table 2b.

Fig. 2



Change from baseline in PANSS hostility score during 6 weeks of treatment with lurasidone vs. placebo. (a) Adults: baseline hostility ≥2. MMRM with baseline hostility scores as a covariate (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$). (b) Early-onset, ages 13–25: baseline hostility score ≥2. MMRM with baseline hostility scores as a covariate (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$). MMRM, mixed-effects model for repeated-measures; PANSS, Positive and Negative Syndrome Scale.

Early-onset: Lack of effect of somnolence on anti-hostility effect of lurasidone

Week 6 P7 hostility change scores were similar after adjustment for PANSS-positive symptoms and after adjustment for both PANSS-positive symptoms and somnolence, respectively, in the baseline hostility ≥2 group (placebo: −0.44, −0.48; lurasidone 40 mg: −0.67, −0.70; lurasidone 80 mg: −0.99, −1.02; and lurasidone 120/160 mg: −0.81, −0.83). Adding somnolence as a covariate had similarly minimal effects on week 6 hostility change scores in the baseline hostility ≥3 and ≥4 groups.

Discussion

The results of these post hoc analyses suggest that treatment with lurasidone may be a significantly effective treatment for hostility in patients experiencing an acute exacerbation of schizophrenia. In the adult population, improvement in hostility on lurasidone was evident in all three hostility severity subgroups, with a trend evident for larger adjusted effect sizes (vs. placebo) as the severity of baseline hostility scores increased (≥2, ≥3, ≥4, respectively) for lurasidone 40 mg (0.03 → 0.03 → 0.28), 80 mg (0.08 → 0.12 → 0.34), 120 mg (0.20 → 0.28 → 0.31), and 160 mg (0.29 → 0.32 → 0.53). Within each hostility severity subgroup, there was a dose–response effect, with larger effect sizes generally observed at the higher (120–160 mg) versus lower (40–80 mg) doses of lurasidone. As expected, adjustment for the covariate effects of lurasidone on PANSS-positive symptoms and somnolence reduced the week 6 effect sizes for all 4 doses of lurasidone by approximately 30–40%, consistent with a partial correlation between the P7 hostility score and the overall PANSS-positive subscale.

In early-onset patients with schizophrenia (ages 13–25), improvement in hostility during treatment with lurasidone exhibited a similar pattern, both in terms of the dose–response effect, and in terms of the larger magnitude of the treatment effect of lurasidone observed in the higher hostility severity subgroups (effect size vs. placebo). Across all three severity subgroups, the magnitude of improvement in hostility on lurasidone was larger (effect size difference score >0.20) for patients with early-onset schizophrenia compared to the adult subgroup.

Regarding the time-to-onset of the anti-hostility treatment effect, significant separation from placebo was predominantly observed at week 1 for the higher doses of lurasidone and at week 2 for the lower doses in both the adult and early-onset groups.

As noted above, adjustment for PANSS-positive symptoms was associated with an approximately 30–40% reduction in week 6 effect size in both the adult and early-onset analysis groups. This reduction was similar in magnitude to the reduction in least squares mean hostility difference scores reported for cariprazine after a similar adjustment (Citrome *et al.*, 2016a,b). Adjustment for the presence of treatment-emergent somnolence-related adverse events had no effect on the anti-hostility treatment effect of lurasidone. Both of these findings are consistent with what has been reported for the anti-hostility effects of other atypical antipsychotics such as clozapine and olanzapine, suggesting that anti-hostility is a specific effect, and not simply a secondary consequence of overall improvement (Volavka *et al.*, 2011, 2014; Citrome and Volavka, 2021).

The effect sizes for lurasidone's anti-hostility effect in patients with a baseline P7 hostility score ≥3, suggest that lurasidone in doses of 120–160 mg is associated with an effect size that is comparable to what has been reported for clozapine, olanzapine, aripiprazole, cariprazine, and asenapine (Volavka *et al.*, 1993, 2004, 2005, Citrome *et al.*, 2016a,b; 2017; Citrome and Volavka., 2021). Prospective, head-to-head comparator trials of patients with hostility item scores ≥3, however, would be required to confirm this tentative estimate of the magnitude of the anti-hostility effect of lurasidone and other atypical antipsychotics.

Limitations

The principal limitation of this study is that it is post hoc and that patients were not specifically selected because they were hostile or aggressive. Patients did provide informed consent to participate in a placebo-controlled clinical trial, and hence may not be entirely representative of the patient population routinely presenting for treatment at a hospital or clinic. Dosing of lurasidone among patients less than 18 years was limited to 40 or 80 mg/day. The short duration of the included studies preclude any discussion of enduring or long-term therapeutic effects.

Conclusion

The results of this post hoc analysis suggest that lurasidone may be an effective treatment for hostility in patients with schizophrenia, especially at higher doses. Lurasidone demonstrated specific improvement in symptoms of hostility that was observed independent of change in other positive symptoms of schizophrenia or the presence of somnolence/sedation. A clinically important finding was the increased anti-hostility efficacy observed for lurasidone in patients with the highest level of baseline hostility, since these individuals represent an especially at-risk group for aggressive behaviors, nonadherence with treatment, and the potential for violence.

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Conflicts of interest

L.C. has received consulting fees from AbbVie/Allergan, Acadia, Adamas, Alkermes, Angelini, Astellas, Avanir, Axsome, Biogen, BioXcel, Boehringer Ingelheim, Cadent Therapeutics, Cerevel, Clinilabs, COMPASS, Delpor, Eisai, Enteris BioPharma, HLS Therapeutics, Idorsia, INmune Bio, Impel, Intra-Cellular Therapies, Janssen, Karuna, Lundbeck, Luye, Lyndra, MapLight, Marvin, Medavante-ProPhase, Merck, Mitsubishi-Tanabe Pharma, Neumora, Neurocrine, Neurelis, Noema, Novartis, Noven, Otsuka, Ovid, Praxis, Recordati, Relmada, Reviva, Sage, Sumitomo/Sunovion, Supernus, Teva, University of Arizona, Vanda, Wells Fargo, and

one-off ad hoc consulting for individuals/entities conducting marketing, commercial, or scientific scoping research; served as speaker for AbbVie/Allergan, Acadia, Alkermes, Angelini, Axsome, BioXcel, Eisai, Idorsia, Intra-Cellular Therapies, Janssen, Lundbeck, Neurocrine, Noven, Otsuka, Recordati, Sage, Sunovion, Takeda, Teva, and CME activities organized by medical education companies such as Medscape, NACCME, NEI, Vindico, and Universities and Professional Organizations/Societies; owns stocks (small number of shares of common stock): Bristol-Myers Squibb, Eli Lilly, J & J, Merck, Pfizer purchased >10 years ago, stock options: Reviva; and received royalties/publishing income from Taylor & Francis (Editor-in-Chief, Current Medical Research and Opinion, 2022-date), Wiley (Editor-in-Chief, International Journal of Clinical Practice, through end 2019), UpToDate (reviewer), Springer Healthcare (book), Elsevier (Topic Editor, Psychiatry, Clinical Therapeutics). I.G.I. and E.A.B., are employees of Angelini Pharma SpA. K.T. is an employee of Medastats LLC. M.T. was an employee of Sumitomo Pharma America, Inc. at the time these data were analyzed and the manuscript was drafted.

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Similar data have been presented in part as posters at the following professional congresses:

Citrome L, Pikalov A, Tocco M, Hsu J, Loebel A. Effects of lurasidone on hostility in patients with an acute exacerbation of schizophrenia: a pooled post hoc analysis of five short-term studies. Poster presentation, American College of Neuropsychopharmacology 53rd Annual Meeting, Phoenix, Arizona, 7–11 December 2014. Abstract in Neurosychopharmacology 39(S1):S379–S380, 2014.

Citrome L, Pikalov A, Tocco M, Hsu J, Loebel A. Effects of lurasidone on hostility in patients with an acute exacerbation of schizophrenia: a pooled post hoc analysis of five short-term studies. Poster presentation, 15th International Congress on Schizophrenia Research, Colorado Springs, Colorado, 28 March–1 April, 2015. Abstract in Schizophrenia Bulletin 41(S1):S306, 2015.

Citrome L, Pikalov A, Tocco M, Hsu J, Loebel A. Effects of lurasidone on hostility in patients with an acute exacerbation of schizophrenia: a pooled post hoc analysis of five short-term studies. Oral presentation, 23rd European Congress of Psychiatry, Vienna, Austria, 28–31 March 2015.

Citrome L, Pikalov A, Tocco M, Hsu J, Loebel A. Effects of lurasidone on hostility in patients with an acute exacerbation of schizophrenia: a pooled post hoc analysis of five short-term studies. Poster presentation, College of Psychiatric and Neurologic Pharmacists, Tampa, Florida, 19–22 April 2015.

Citrome L, Pikalov A, Tocco M, Hsu J, Loebel A. Effects of lurasidone on hostility in patients with an acute exacerbation of schizophrenia: a pooled post hoc analysis of five short-term studies. Poster presentation, American Society of Clinical Psychopharmacology Annual Meeting, Miami, Florida, 22–25 June 2015.

Citrome L, Gabarda I, Alvarez-Baron E, Rosignoli MT, Mao Y, Tocco M. The effect of lurasidone on hostility in adults with an acute exacerbation of schizophrenia. European College of Neuropsychopharmacology Congress, Barcelona, Spain, 7–10 October 2023.

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