

A Clinical Research Program for the Treatment of Schizoaffective Disorder: Study Designs and Subject Characteristics

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ABSTRACT

Background: Although schizophrenia and bipolar disorder have been the focus of extensive clinical research, schizoaffective disorder remains an understudied condition. Key design elements and demographic and clinical characteristics are presented from the first registration program of subjects with schizoaffective disorder.

Methods: The sources of the subject characteristics were two international, double-blind, placebo-controlled studies assessing paliperidone extended-release (ER) in subjects with schizoaffective disorder. Subjects met SCID-confirmed DSM-IV criteria for schizoaffective disorder; Positive and Negative Syndrome Scale (PANSS) total score ≥ 60 , a score ≥ 4 on two or more PANSS items of hostility, excitement, tension, uncooperativeness and poor impulse control; and prominent mood symptoms (≥ 16 Young Mania Rating Scale [YMRS] and/or Hamilton Rating Scale for Depression, 21-Item version [HAM-D-21]). Stable doses of antidepressants/mood stabilizers were permitted if given within 30 days of screening. Assessments included the PANSS (primary), the novel Clinical Global Impressions–Severity for Schizoaffective Disorder (CGI-S-SCA), the YMRS and the HAM-D-21.

Results: 614 subjects were in the combined ITT population; 40.4% were from the US and 59.6% were ex-US. The mean age of the population was 37.4 years (range 18-61); 60.4% were male and 48.9% were Caucasian. Mean ages at first psychiatric and first schizoaffective disorder diagnoses were 25.2 (range 4-56) years and 31.7 (range 3-61) years, respectively. Approximately 45% of subjects were taking concomitant antidepressants and/or mood stabilizers. 68.9% of subjects were diagnosed with bipolar type of schizoaffective disorder and 31.1% were diagnosed with depressive type. 31.4% of subjects had attempted suicide in their lifetime; 47.9% of those subjects made at least two attempts. Mean (SD) baseline PANSS total score was 92.8 (12.9). Mean (SD) baseline CGI-S-SCA score was 4.6 (0.6) (range 3.0-6.0). The percentages of subjects with YMRS ≥ 16 or HAM-D-21 ≥ 16 at baseline were 79.5% and 66.9%, respectively; 46.4% had both scores ≥ 16 . In subjects with prominent manic or depressive symptoms, mean (SD) baseline YMRS and HAM-D-21 scores were 28.1 (7.5) and 25.0 (6.3), respectively.

Conclusions: This population presented with the full range of psychotic and affective symptoms characteristic of schizoaffective disorder. Findings suggest that a schizoaffective diagnosis is often preceded by an earlier diagnosis of another psychiatric disorder. Further, these data suggest that these subjects are frequently treated with concomitant psychotropic medications, often experience repeated hospitalizations and carry a high suicide risk.

INTRODUCTION

- Schizoaffective disorder is characterized by an uninterrupted period of illness during which the patient must experience a major depressive, manic or mixed episode concurrent with the positive (delusions, hallucinations and disorganized speech and behavior) and negative symptoms of schizophrenia.¹
- The lifetime prevalence of schizoaffective disorder is 0.3% to 0.8%^{2,3} and is approximately one-third as common as schizophrenia.⁴ However, the incidences of schizoaffective disorder and schizophrenia among frequent users of mental health services are approximately 24% and 32%, respectively.⁵
- Additionally, use of concomitant medications in this patient population is high; recent studies indicate that up to 87% of patients with schizoaffective disorder are treated with antipsychotics in combination with a mood stabilizer or antidepressant.⁶
- Despite its prevalence, chronic nature and the lifelong need for pharmacotherapy, there are no clear guidelines for the treatment of schizoaffective disorder; further, there are no established approaches for its study in clinical trials.
- This poster presents key design elements from the first registration program in schizoaffective disorder as well as the demographic and clinical characteristics of the population at study entry.

METHODS

Schizoaffective Disorder Clinical Research Program

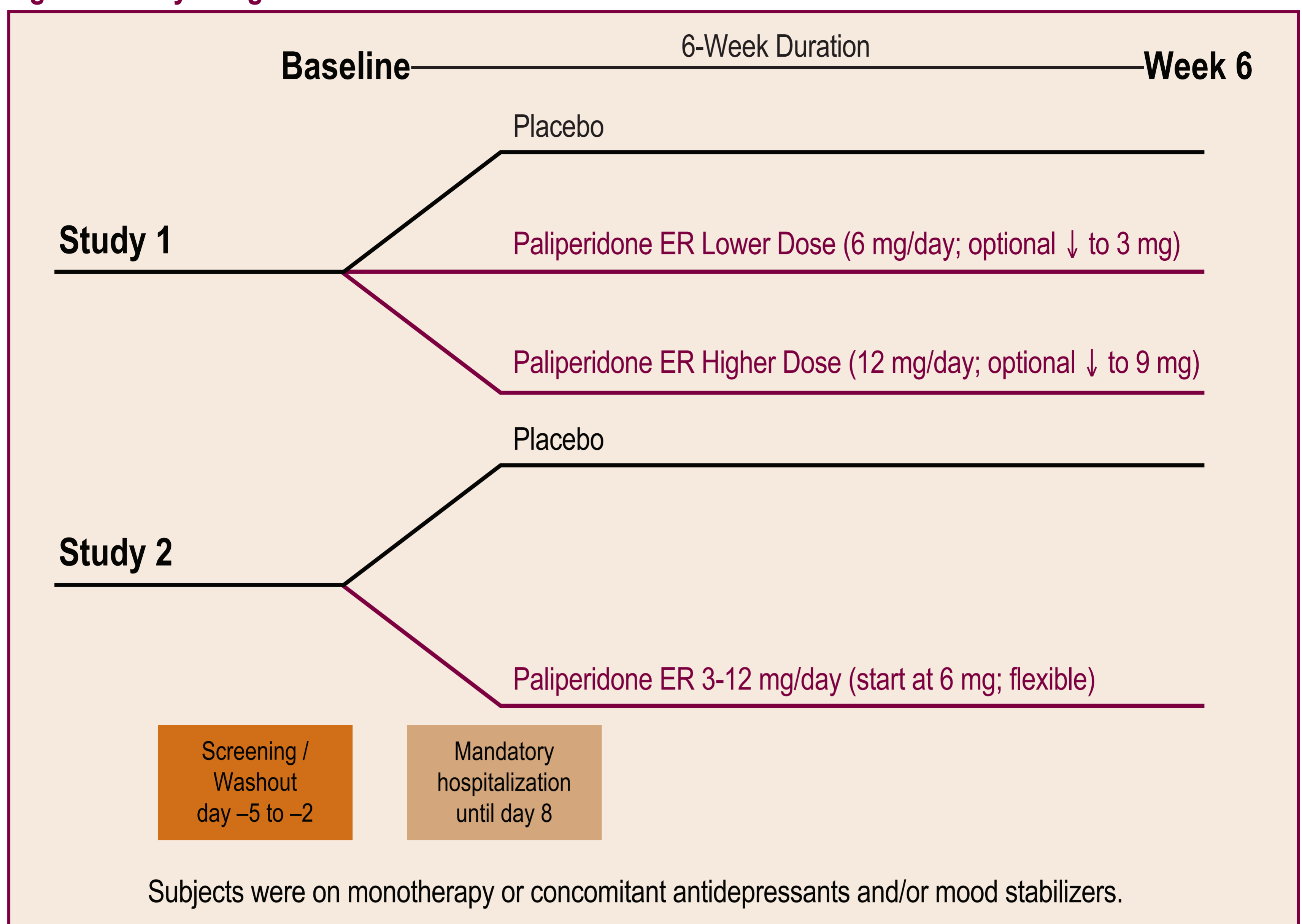
Study Designs (Figure 1)

- As a novel indication, consultation on the methodology was obtained from the FDA through the Special Protocol Assessment process.
- Investigators participated in comprehensive training on the course of schizoaffective disorder, application of the Structured Clinical Interview for DSM-IV (SCID), and use of rating instruments, including a new disease-specific rating scale called the Clinical Global Impressions of Severity for Schizoaffective Disorder (CGI-S-SCA).
- To reflect typical clinical practice, subjects both with and without concomitant antidepressants and mood stabilizers were included in the studies.
- **Study 1**
 - Multicenter, international, randomized, double-blind, placebo-controlled, parallel-group study. Study ID: CR010498
 - Subjects with a SCID-confirmed diagnosis of schizoaffective disorder who were experiencing an acute exacerbation were randomized in a 1:1:1 ratio to receive lower-dose paliperidone extended-release (ER) (6 mg/day, option to reduce to 3 mg/day), higher-dose paliperidone ER (12 mg/day, option to reduce to 9 mg/day) or placebo.
 - No dosage adjustments were permitted after the day 15 visit.
- **Study 2**
 - Multicenter, international, randomized, double-blind, placebo-controlled, parallel-group study. Study ID: CR013099
 - Subjects with an established diagnosis of schizoaffective disorder who were experiencing an acute exacerbation were randomized in a 2:1 ratio to receive 6 mg/day of paliperidone ER or placebo. After day 4, a subject's dose could be adjusted in 3-mg increments in a range of 3-12 mg/day until day 15.
 - No dosage adjustments were permitted after the day 15 visit.
- Subjects from both studies were permitted to receive concomitant treatment with antidepressants and/or mood stabilizers provided that these medications had been given at a stable dose within 30 days of screening.
- Randomization was stratified by center and by treatment with concomitant medications (with vs without antidepressants and/or mood stabilizers).

Inclusion Criteria (Both Studies)

- Men and women aged 18 to 65 years
- Subjects with an acute exacerbation who met the DSM-IV criteria for schizoaffective disorder as confirmed by SCID
- Positive and Negative Syndrome Scale (PANSS) total score of at least 60 and a score ≥ 4 on at least two of the following PANSS items: hostility (P7), excitement (P4), tension (G4), uncooperativeness (G8) and poor impulse control (G14)
- Prominent mood symptoms: score ≥ 16 on the Young Mania Rating Scale (YMRS) and/or on the Hamilton Rating Scale for Depression, 21-item version (HAM-D-21)

Figure 1. Study Designs.



Endpoints (Both Studies)

- **Primary study endpoint:** change in the PANSS total score from baseline to week 6 end point (last observation carried forward [LOCF]) for each paliperidone ER group vs placebo
- **Selected secondary endpoints:** CGI-S-SCA total score, YMRS, HAM-D-21, InterSePT Scale for Suicidal Thinking (ISST)

Baseline Demographic and Clinical Characteristics

- This pooled baseline analysis used descriptive statistics to evaluate the demographics and clinical characteristics of the population.
- Concomitant medications of interest were also evaluated.
 - Defined as antidepressants and/or mood stabilizers used for ≥75% of the time during the studies
- **Analysis set used:** intent-to-treat (ITT)—all randomized subjects who received at least one dose of study medication and who had both baseline and at least one post-baseline PANSS assessment

RESULTS

Table 1. Analysis Sets.

	Study 1	Study 2	Total Population
Number of subjects randomized, N	316	311	627
Number of subjects in ITT analysis set, N	310	304	614
Number of ITT subjects by concomitant medication stratum			
Treatment with antidepressants and/or mood stabilizers	117	158	275
No treatment with antidepressants and/or mood stabilizers	193	146	339
Number of subjects randomized by country			
India	100	39	139
Malaysia	N/A	16	16
Philippines	N/A	22	22
Romania	N/A	82	82
South Korea	N/A	12	12
Russia	36	N/A	36
Ukraine	63	N/A	63
United States	117	140	257

Demographics, Psychiatric History and Concomitant Medications

- The analysis sets of these studies are outlined in **Table 1**.
- The mean age of the total population was 37.4 years (range 18-61); 60.4% were male and 48.9% were Caucasian (**Table 2**).
- 40.4% of the population were from the United States and 59.6% were from outside the United States.
- The mean (SD) ages at first psychiatric and schizoaffective disorder diagnoses were 25.2 (9.3) and 31.7 (10.2) years, respectively.
- 68.9% of subjects were diagnosed with the bipolar subtype of schizoaffective disorder and 31.1% were diagnosed with the depressive subtype.
- 90.9% had a clinical diagnosis of schizoaffective disorder prior to screening.
- Almost half of the subjects (49.4%) had more than three psychiatric hospitalizations prior to enrollment.
- 31.4% of subjects had attempted suicide in their lifetime, with 47.9% of those subjects having made at least two attempts.
- 44.8% of total subjects were taking concomitant antidepressants and/or mood stabilizers (**Figure 2**).

Table 2. Demographic Characteristics and Psychiatric History (ITT Analysis Set).

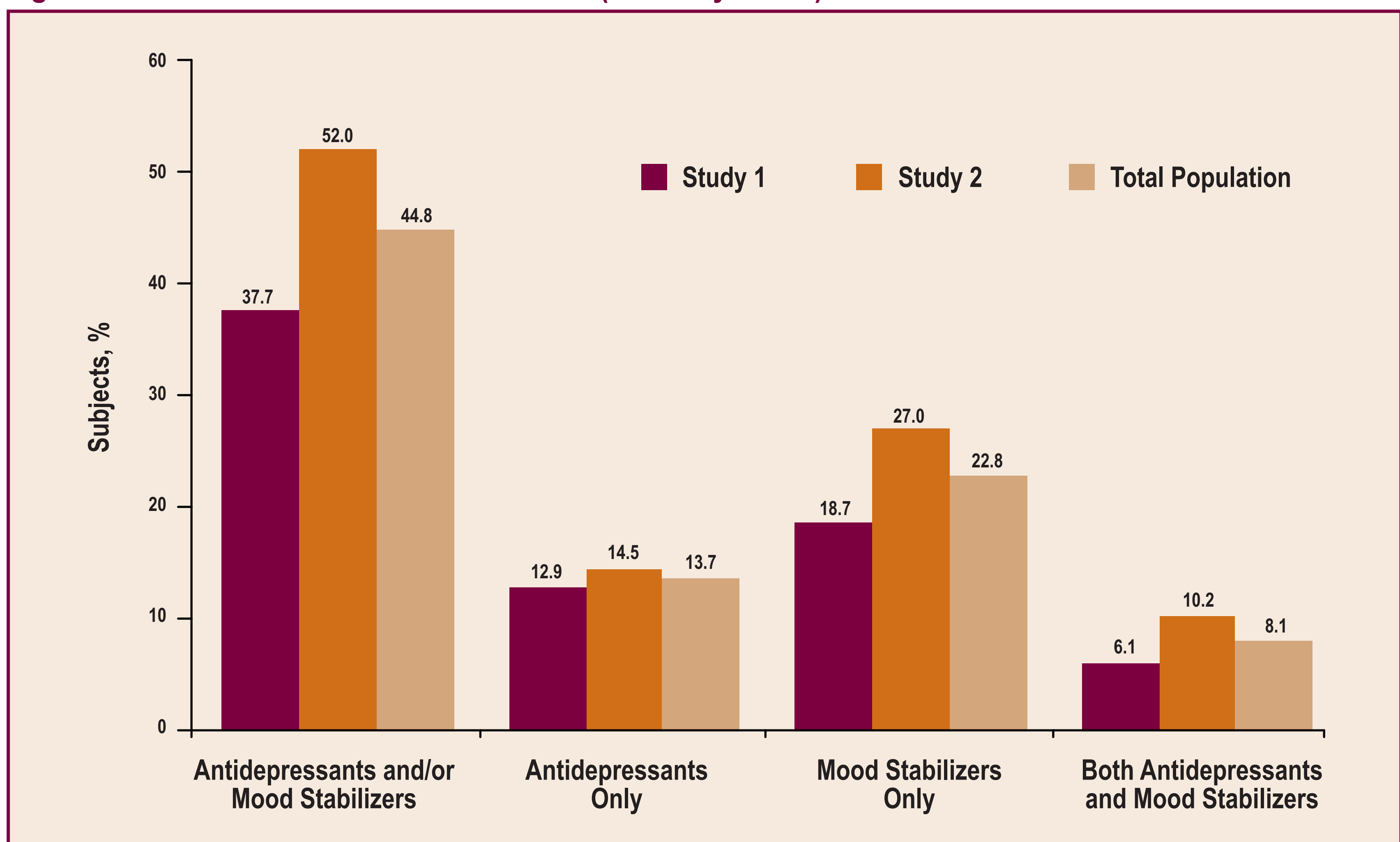
	Study 1 N = 310	Study 2 N = 304	Total Population N = 614
Age, years, mean (SD)	37.3 (10.5)	37.6 (9.2)	37.4 (9.9)
Gender, male, n (%)	201 (64.8)	170 (55.9)	371 (60.4)
Race, n (%)			
Caucasian	144 (46.5)	156 (51.3)	300 (48.9)
Asian	102 (32.9)	90 (29.6)	192 (31.3)
African American	63 (20.3)	55 (18.1)	118 (19.2)
American Indian or Alaska Native	1 (0.3)	1 (0.3)	2 (0.3)
Other	0 (0)	2 (0.7)	2 (0.3)
Body mass index, kg/m ² , mean (SD)*	26.7 (6.9)	28.3 (7.8)	27.5 (7.4)
Age at first psychiatric diagnosis, years, mean (SD)*	26.1 (10.1)	24.3 (8.3)	25.2 (9.3)
Age at first SCA diagnosis, years, mean (SD)*	32.5 (10.7)	30.8 (9.5)	31.7 (10.2)
SCA subtype, n (%)*			
Depressive	95 (30.9)	95 (31.3)	190 (31.1)
Bipolar	212 (69.1)	209 (68.8)	421 (68.9)
Other prior psychiatric diagnoses, n (%)†			
Schizophrenia	146 (47.1)	144 (47.4)	290 (47.2)
Bipolar disorder	95 (30.6)	95 (31.3)	190 (30.9)
Depression	53 (17.1)	59 (19.4)	112 (18.2)
SCA diagnosis prior to screening, n (%)*	276 (90.2)	272 (91.6)	548 (90.9)
History of substance abuse, yes, n (%)	86 (27.7)	97 (31.9)	183 (29.8)
Age at first psychiatric hospitalization, years mean (SD)*	28.3 (10.4)	26.1 (9.2)	27.2 (9.9)
Psychiatric hospitalizations, mean (SD)*	4.3 (5.8)	8.4 (10.1)	6.3 (8.4)
Total number, n (%)			
0	63 (20.6)	27 (9.0)	90 (14.9)
1	53 (17.3)	33 (11.0)	86 (14.2)
2	47 (15.4)	31 (10.4)	78 (12.9)
3	31 (10.1)	21 (7.0)	52 (8.6)
>3	112 (36.6)	187 (62.5)	299 (49.4)
Attempted suicide, yes, n (%)*	80 (25.8)	112 (37.1)	192 (31.4)
Number of attempts, n (%)			
1	46 (57.5)	54 (48.2)	100 (52.1)
≥2	34 (42.5)	58 (51.8)	92 (47.9)

SCA = schizoaffective disorder.

*Sample sizes are less than ITT population due to missing values.

†Data are not mutually exclusive.

Figure 2. Concomitant Medications of Interest (ITT Analysis Set).*



*Data were not available for one subject in Study 2 for whether he/she received antidepressants only, mood stabilizers only or both.

Baseline Clinical Measures

- Mean (SD) baseline PANSS total score 92.8 (12.9) (**Table 3**)
- The mean (SD) baseline CGI-S-SCA score was 4.6 (0.6), with the majority of subjects classified as moderately (43.0%) or markedly ill (49.0%).
- The percentages of subjects with YMRS ≥ 16 or HAM-D-21 ≥ 16 at baseline were 79.5% and 66.9%, respectively (**Figure 3**). The percentage of subjects with both YMRS and HAM-D-21 ≥ 16 at baseline was 46.4%.
- Mean (SD) scores for the YMRS and HAM-D were 24.4 (10.0) and 20.1 (8.8), respectively.
- Clinical characteristics were similar between subjects with prominent manic or depressive symptoms, although this may be a result of the study inclusion criteria (**Table 4**).

Table 3. Baseline Clinical Measures (ITT Analysis Set).

	Study 1 N = 310	Study 2 N = 304	Total Population N = 614
Baseline PANSS scores, mean (SD)			
Total	93.4 (12.8)	92.1 (13.1)	92.8 (12.9)
Positive factor	27.2 (5.1)	27.4 (5.3)	27.3 (5.2)
Negative factor	18.6 (5.8)	18.6 (6.3)	18.6 (6.1)
Disorganized thoughts	20.1 (4.0)	19.0 (4.2)	19.5 (4.1)
Uncontrolled hostility/excitement	14.6 (2.9)	13.8 (3.1)	14.2 (3.0)
Anxiety/depression	12.9 (3.7)	13.3 (3.7)	13.1 (3.7)
Baseline YMRS, mean (SD)	25.7 (10.0)	23.1 (10.0)	24.4 (10.0)
Baseline HAM-D-21, mean (SD)	20.1 (9.2)	20.2 (8.3)	20.1 (8.8)
Baseline CGI-S-SCA, mean (SD)	4.6 (0.6)	4.6 (0.7)	4.6 (0.6)
Category, n (%)			
Mildly ill	3 (1.0)	4 (1.3)	7 (1.1)
Moderately ill	134 (43.2)	130 (42.8)	264 (43.0)
Markedly ill	156 (50.3)	145 (47.7)	301 (49.0)
Severely ill	17 (5.5)	25 (8.2)	42 (6.8)
Baseline ISST, n (%)*			
≥ 1	55 (27.0)	50 (23.8)	105 (25.4)
0	149 (73.0)	160 (76.2)	309 (74.6)

*Study 1: N = 204; Study 2: N = 210; total population N = 414.

Figure 3. Percentages of Subjects With Prominent Mood Symptoms (ITT Analysis Set).

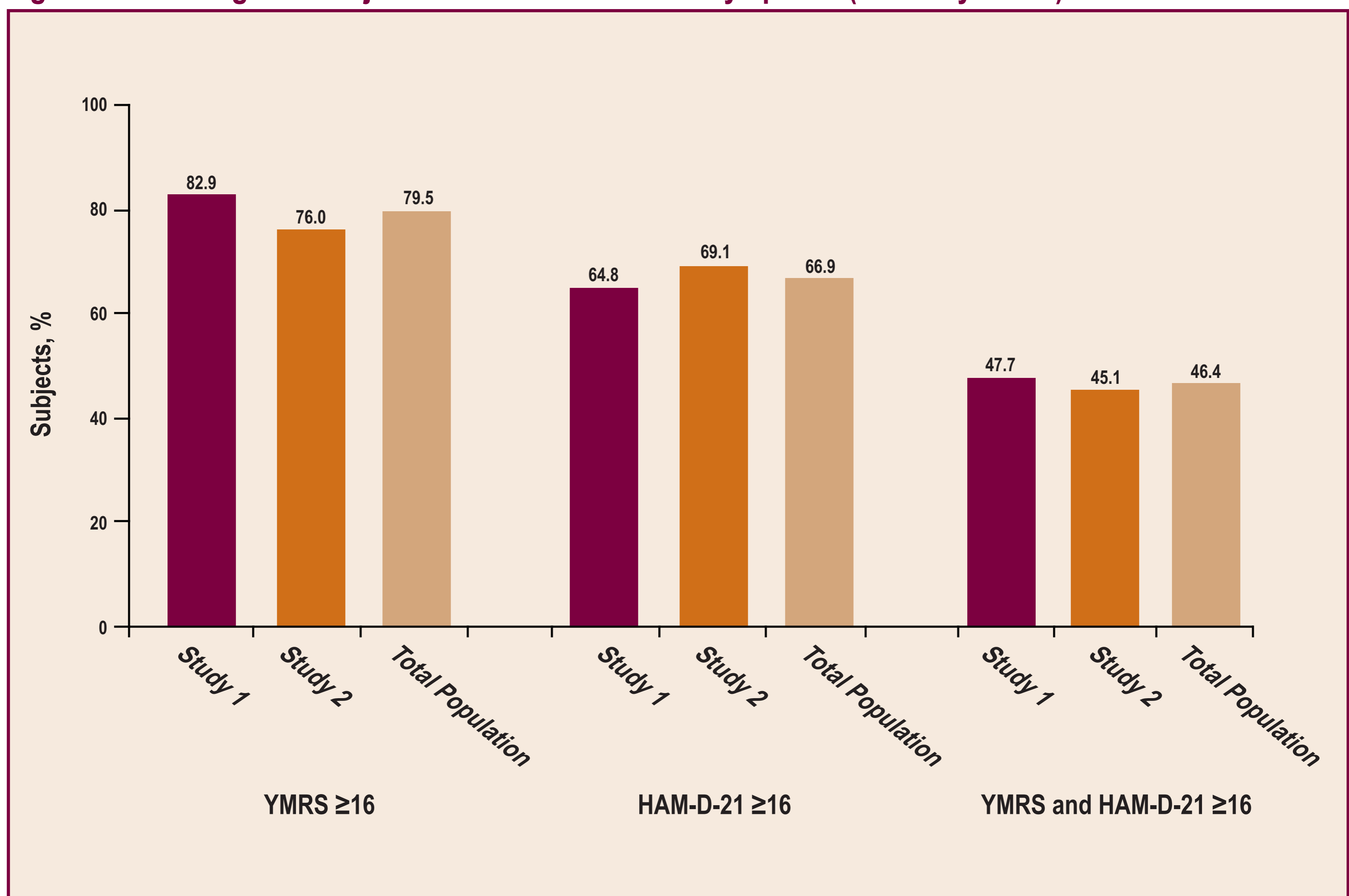


Table 4. Clinical Characteristics of Subjects With Prominent Affective Symptomatology (ITT Analysis Set).

	YMRS ≥16 N = 488	HAM-D-21 ≥16 N = 411
Age, years, mean (SD)	37.6 (10.0)	37.3 (9.9)
Gender, male, n (%)	300 (61.5)	230 (56.0)
SCA subtype, n (%) [*]		
Depressive	94 (19.4)	186 (45.6)
Bipolar	391 (80.6)	222 (54.4)
Other prior psychiatric diagnoses [†]		
Schizophrenia	240 (49.2)	196 (47.7)
Bipolar disorder	163 (33.4)	121 (29.4)
Depression	84 (17.2)	97 (23.6)
SCA diagnosis prior to screening, n (%) [*]	438 (91.1)	369 (91.8)
Attempted suicide, yes, n (%) [*]	152 (31.3)	152 (36.7)
Number of attempts, n (%)		
1	79 (52.0)	75 (49.3)
≥2	73 (48.0)	77 (50.7)
Baseline YMRS, mean (SD)	28.1 (7.5)	21.6 (10.2)
Baseline HAM-D-21, mean (SD)	18.7 (8.9)	25.0 (6.3)
YMRS ≥16, n (%)	488 (100)	285 (69.3)
HAM-D-21 ≥16, n (%)	285 (58.4)	411 (100)
Baseline total PANSS scores, mean (SD)	92.7 (13.2)	95.8 (12.6)
Baseline CGI-S-SCA score, mean (SD)	4.7 (0.6)	4.7 (0.6)

^{*}Sample sizes are less than ITT population due to missing values.

[†]Data are not mutually exclusive.

DISCUSSION

- The baseline characteristics of this population reflect severe psychotic symptoms coupled with prominent affective symptoms; the severity of affective symptoms substantially exceeded the minimum entry criteria for both the YMRS and HAM-D.
- The mean time interval between first psychiatric diagnosis and first schizoaffective disorder diagnosis of 6.5 years suggests a period of evolution to reach the diagnosis of schizoaffective disorder.
 - This may be due to the emergent awareness of the diagnosis for clinicians and the need for careful diagnostic history.
- The majority of subjects carried a clinical diagnosis of schizoaffective disorder at study entry, prior to receiving the SCID diagnosis.
- Due to entry criteria, there may be over-representation of the bipolar subtype, yet a large proportion of subjects presented with prominent depressive symptomatology.
- There was generally a balance between subjects who received paliperidone ER as monotherapy and those who received it in combination with antidepressants and/or mood stabilizers.

CONCLUSIONS

- To our knowledge, this clinical program represents the first registration trials focused exclusively on subjects with schizoaffective disorder. Key design elements include: rigorous diagnostic assessment of subjects, a novel rating scale to measure the varied symptom domains of this illness, and evaluation of subjects with and without mood stabilizers and/or antidepressants reflecting typical clinical practice.
- This population presented with the full range of psychotic and affective symptoms characteristic of schizoaffective disorder. Findings suggest that a schizoaffective diagnosis is often preceded by an earlier diagnosis of another psychiatric disorder. Further, data suggest that these subjects often experience repeated hospitalizations and carry a high risk of suicide.
- Further analyses exploring distinctions between schizoaffective disorder and schizophrenia and bipolar disorder are warranted.

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