Safety of Paliperidone Extended-Release in Patients with Schizophrenia or Schizoaffective Disorder and Hepatic Disease

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Abstract

Background/Purpose: Patients with schizophrenia often suffer from comorbid hepatic disease. This multicenter, open-label, single-arm, crossover study evaluated the safety and efficacy of paliperidone extended-release (ER) in patients with schizophrenia or schizoaffective disorder and hepatic disease. **Methods:** The study comprised a screening period, followed by 9 weeks' open-label treatment, divided into 2 phases. Phase 1 (4 weeks) was a continuation of usual antipsychotic treatment (UAT); phase 2 (5 weeks) consisted of a 1-week cross-titration from UAT to flexibly dosed paliperidone ER (3–12 mg/d), followed by 4 weeks of paliperidone ER alone. Treatment-emergent adverse events (TEAEs), including those considered more relevant to antipsychotic treatment (prespecified adverse events [AEs]), were analyzed. **Results:** Although more subjects reported TEAEs during the paliperidone ER alone period than during the UAT period, no significant differences occurred in prespecified AE rates. No new safety signals were detected, and minimal shifts in liver function test values were observed. Improvements in psychiatric symptoms and functioning were observed after 4 weeks' paliperidone ER treatment. **Conclusions:** This study suggests that paliperidone ER is well tolerated in patients with schizophrenia or schizoaffective disorder and hepatic disease. To the best of our knowledge, this is the largest prospective study to date in this population.

Key Words: Paliperidone ER, Hepatic Disease, Schizophrenia, Atypical Antipsychotic

Introduction

Patients with schizophrenia often have comorbid hepatic disease (1-3). Factors contributing to the risk of hepatic disease in these patients include alcohol abuse, leading to cirrhosis (4-6), and injection drug use or high-risk sexual activity, resulting in increased risk of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection. HBV and HCV are major causes of cirrhosis, hepatic decompensation, and hepatocellular carcinoma (7, 8). Patients with schizophrenia tend to receive low-quality care or do not seek care at all, further compounding their risk (9).

Several retrospective database analyses found significantly higher rates of hepatic disease in patients with mental illness than in the general population. One medical claims study comparing patients with schizophrenia with all other patients in the database found those with schizophrenia had 7.54 times higher risk of HCV infection; 4.42 times higher risk of hepatic disease; 12.57 times higher risk of alcohol use/dependence; and, 35.42 times higher risk of illegal drug use (10). Another retrospective database analysis found that after standardizing differences in age, sex, and race, treated hepatic disease occurred in a higher proportion of patients

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Clinical Implications

The results of this exploratory, open-label, single-arm, crossover study suggest that paliperidone extended release (ER) is well tolerated in patients with schizophrenia or schizoaffective disorder who have stable active hepatic disease. No new safety signals were detected in this hepatically compromised patient population. Improvements in psychiatric symptoms and patient functioning were observed after four weeks of treatment with paliperidone ER. A future controlled study with placebo or an active comparator could be conducted to further test the hypothesis that paliperidone ER, with its limited hepatic metabolism, has a favorable risk-benefit profile for patients with schizophrenia or schizoaffective disorder and comorbid hepatic disease.

with schizophrenia than in the non-mentally ill comparison group (4.6 vs. 4.1%; p<0.001) or in the historical general population (1.3%) (11). Another study in patients with severe mental illness reported prevalence of HBV (23.4%) and HCV (19.6%) infection to be 5 to 11 times the overall estimated population prevalence for these infections (2).

Patients with schizophrenia or schizoaffective disorder are frequently treated with multiple psychotropic medications, mostly metabolized in the liver (12). Antipsychotics are essential for treating symptoms, but when patients have comorbid conditions altering hepatic function, drug metabolism may be impaired (13). Without dose adjustment, these drug metabolism changes could increase plasma concentration and subsequent drug activity, resulting in toxic effects (14).

Paliperidone extended-release (ER) is an atypical antipsychotic that, unlike other antipsychotics, is not extensively metabolized in the liver (15). A pharmacokinetic analysis in patients with moderate hepatic impairment and healthy volunteers showed that unbound plasma concentrations of paliperidone ER were similar between the populations (16). Consequently, no dose adjustment is required in patients with mild or moderate hepatic impairment. Also, a recent case report suggested that paliperidone may be effective for these patients (17).

The primary objective of this study was to evaluate the tolerability and safety of flexibly dosed paliperidone ER in patients with schizophrenia or schizoaffective disorder with comorbid hepatic disease. The secondary objective was to evaluate the efficacy of paliperidone ER in this patient population.

Methods

This exploratory, multicenter, nine-week, open-label, single-arm, crossover study (study CR014341) was conducted at sixteen centers in the United States in accordance with the Declaration of Helsinki and Good Clinical Reporting Practice. The protocol was approved by an institutional review board for each center. All subjects gave informed consent after the study procedures had been fully explained. The study was registered with clinicaltrials.gov (http://clinicaltrials.gov/ct2/show/NCT00535145) and assigned the registration number NCT00535145.

Subjects

Eligible subjects (18 to 65 years old, inclusive) had a current diagnosis of schizophrenia (paranoid, disorganized, undifferentiated, or residual type) or schizoaffective disorder, according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition *(DSM-IV)*, and a diagnosis of stable active hepatic disease (e.g., chronic hepatitis or cirrhosis), with Child-Pugh classifications of A (well compensated) or B (significant functional compromise) (18). If the hepatic disease was due to viral hepatitis, subjects must have had prior laboratory test documentation or be willing to undergo such testing as part of the screening procedures for this study. All subjects were required to have an aspect of disease management for which change in antipsychotic medication might possibly provide benefit.

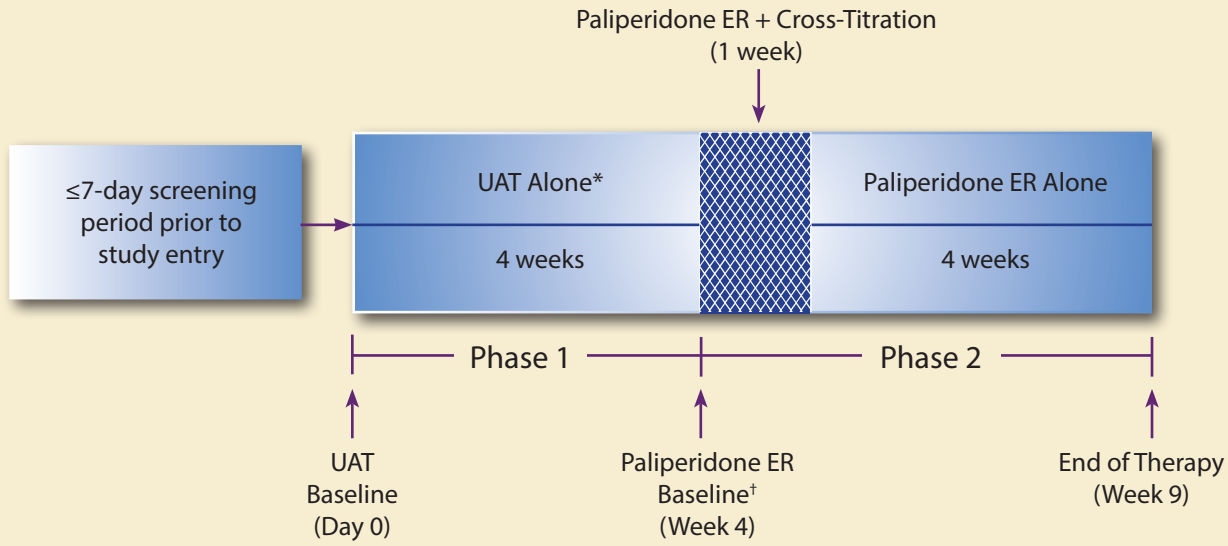
Since paliperidone ER had only been studied in subjects with mild and moderate hepatic impairment (Child-Pugh class B) (16), dosing of paliperidone ER has not been established for patients with severe hepatic impairment. Further, due to the sequelae of hepatic disease per se, inclusion of subjects with severe hepatic impairment could confound the study results, particularly the frequency and types of adverse events. As a result, subjects were excluded if they had characteristics of severe hepatic impairment at screening or at visit 5 (day 27). Severe hepatic impairment included severe hepatic disease, an acute exacerbation of underlying hepatic disease (Child-Pugh total score ≥10), or ≥1 abnormality among the following laboratory parameters: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times the upper limit of normal (ULN); alkaline phosphatase >2 times the ULN; albumin <2.5 g/dL; total bilirubin >3 mg/dL; or sodium <130 mEq/L. Subjects also were excluded if they had had a substantive change in dosing regimen <4 weeks before screening for any medication, with meaningful potential to exacerbate or alter hepatic or psychiatric symptoms (e.g., interferon, rifaximin, lactulose, valproate, carbamazepine, phenytoin, antidepressants). Subjects were also excluded if they had a Clinical Global Impressions-Severity

(CGI-S) score of <3; active substance abuse or dependence, and/or alcohol abuse within the previous 3 months; use of alcohol in the 2 weeks before study entry; or, a urine drug test result positive for cocaine, opiates (including methadone), or amphetamines at screening.

Design

The study included a 7-day screening period, followed by open-label treatment for 9 weeks, divided into 2 phases (see Figure 1). Phase 1 lasted 4 weeks (days 0–27) and was a continuation of usual antipsychotic treatment (UAT), defined as the antipsychotic the subjects were taking before study entry. Phase 2 lasted 5 weeks (days 28–62) and consisted of a 1-week cross-titration from UAT to flexibly dosed paliperidone ER (3–12 mg/d), followed by 4 weeks (days 35–62) of paliperidone ER alone. The stability of hepatic function was assessed by laboratory evaluations of liver function tests (LFTs) at the beginning of each phase.

Figure 1 Study Design



ER=extended-release; UAT=usual antipsychotic treatment.
*UAT began ≥4 weeks before phase 1. †Initiated at 6 mg/d; flexible dosing, 3–12 mg/d.

End Points

Safety assessments included the reporting of treatment-emergent adverse events (TEAEs), prespecified adverse events (AEs), results of clinical laboratory tests (including LFTs), vital sign measurements, electrocardiogram (ECG) assessments, and physical examinations. Hepatic function, including ascites and encephalopathy, was assessed by a gastroenterologist, hepatologist, internist, or family/general practitioner with appropriate medical experience. Prespecified AEs were the subset of AEs that were considered potentially relevant to antipsychotic treatment. They were derived from the AEs listed in the manufacturer's United States (U.S.) Prescribing Information for all antipsychotic medications expected in the study, when such information was available (see Table 1), and included those that occurred at a rate of ≥3% and at ≥1.5 times the rate in placebo. Movement disorders were assessed using the Abnormal Involuntary Movement Scale (AIMS) (19), the Barnes Akathisia Scale (BAS) (20), and the Simpson-Angus Scale (SAS) (21). Sedation was evaluated using a sleep visual analogue scale (VAS).

Efficacy was assessed by the Positive and Negative Syndrome Scale (PANSS) (22), the CGI-S scale (23), the Personal and Social Performance (PSP) scale (24), the Medication Satisfaction Questionnaire (MSQ) (25), and the 36-item Short-Form Health Survey (SF-36) (26). All raters were experienced and had successfully completed a sponsor-approved certification program before participating in the study.

Statistical Analysis

The sample size for this exploratory study was not based on statistical considerations but rather on precedent in the field for studies of special populations, in which samples of approximately 100 subjects were used. Thus, the plan was to recruit sufficient subjects so that approximately 100 subjects would enter phase 2 of the study. The primary safety analysis was a comparison of the incidence of TEAEs between phase 1 and phase 2. This analysis was based on all subjects who received ≥1 dose of paliperidone ER with any safety data from phase 1 and phase 2 (safety analysis set). Phase 1 TEAEs

Table 1 Prespecified Adverse Events by Body System Category

Body System Category	Prespecified Adverse Events*
Central nervous system	Akathisia, dizziness, dystonia, extrapyramidal disorder, gait disturbance, hypertonia, insomnia, parkinsonism, sedation, somnolence, tremor
Gastrointestinal tract	Abdominal discomfort, abdominal pain, constipation, dry mouth, dyspepsia, increased appetite, nausea, salivary hypersecretion, stomach discomfort, vomiting
General (body as a whole)	Back pain, chest pain, fatigue, injury, headache, muscular weakness, pain, pyrexia
Metabolic system and nutrition	Increased alanine aminotransferase, increased aspartate aminotransferase, peripheral edema, increased weight
Musculoskeletal system	Arthralgia, pain in extremity
Psychiatric	Anxiety, restlessness
Respiratory tract	Respiratory tract infection, rhinitis
Vision	Amblyopia, vision blurred, visual disturbance
Other†	Ecchymosis, orthostatic hypotension, rash, tachycardia, urinary tract infection

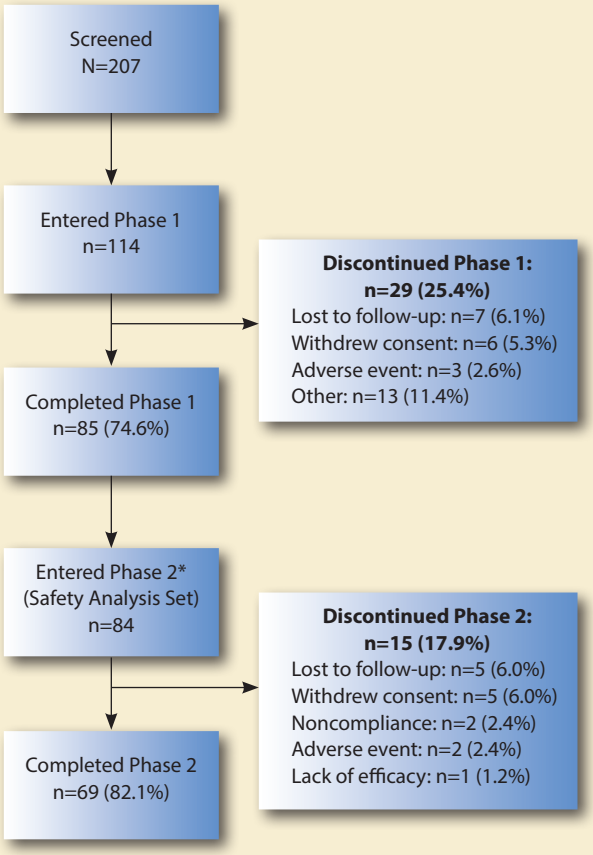
*Prespecified AEs were derived from the AEs listed in the manufacturer's U.S. Prescribing Information for all antipsychotic medications expected in the study, when such information was available, and included those that occurred at a rate of ≥3% and at ≥1.5 times the rate in placebo. †Body system categories with only 1 prespecified AE.

included all events with an onset date from UAT baseline (day 0) to the first dose of paliperidone ER. Phase 2 TEAEs included all events with an onset date from the first dose of paliperidone ER to the last dose of paliperidone ER. In addition, all TEAEs with an onset date during the cross-titration phase were classified as cross-titration events. An additional summary of safety data was also performed on all subjects who entered phase 1 (phase 1 analysis set).

The difference in TEAE incidence between UAT alone and paliperidone ER with or without cross-titration was assessed using AE incidence density (ID) and cumulative mean function (CMF). The TEAE ID per person-month was defined as the number of subjects who experienced ≥1 TEAE in the respective phase divided by the total months those subjects were at risk of experiencing AEs during that phase. The CMF estimates were obtained for the cumulative number of TEAEs per subject in phase 1 and, separately, in phase 2. In the case where multiple AEs occurred on the same day for a given subject, only 1 event was counted for the purpose of calculating CMF. The 95% confidence interval (CI) for differences in the analyses between phase 1 and phase 2 was estimated using bootstrap resampling methodology. If the 95% CIs did not include 0, the between-group comparisons were considered statistically significant at the 5% level.

The efficacy analysis set included all subjects who received paliperidone ER and had efficacy data at paliperidone ER baseline and ≥1 follow-up visit. The changes from UAT baseline (day 0) and from paliperidone ER baseline (day 27) to study end point (day 62) were assessed using paired t tests. No adjustments were made for multiplicity or multiple comparisons.

Figure 2 Disposition



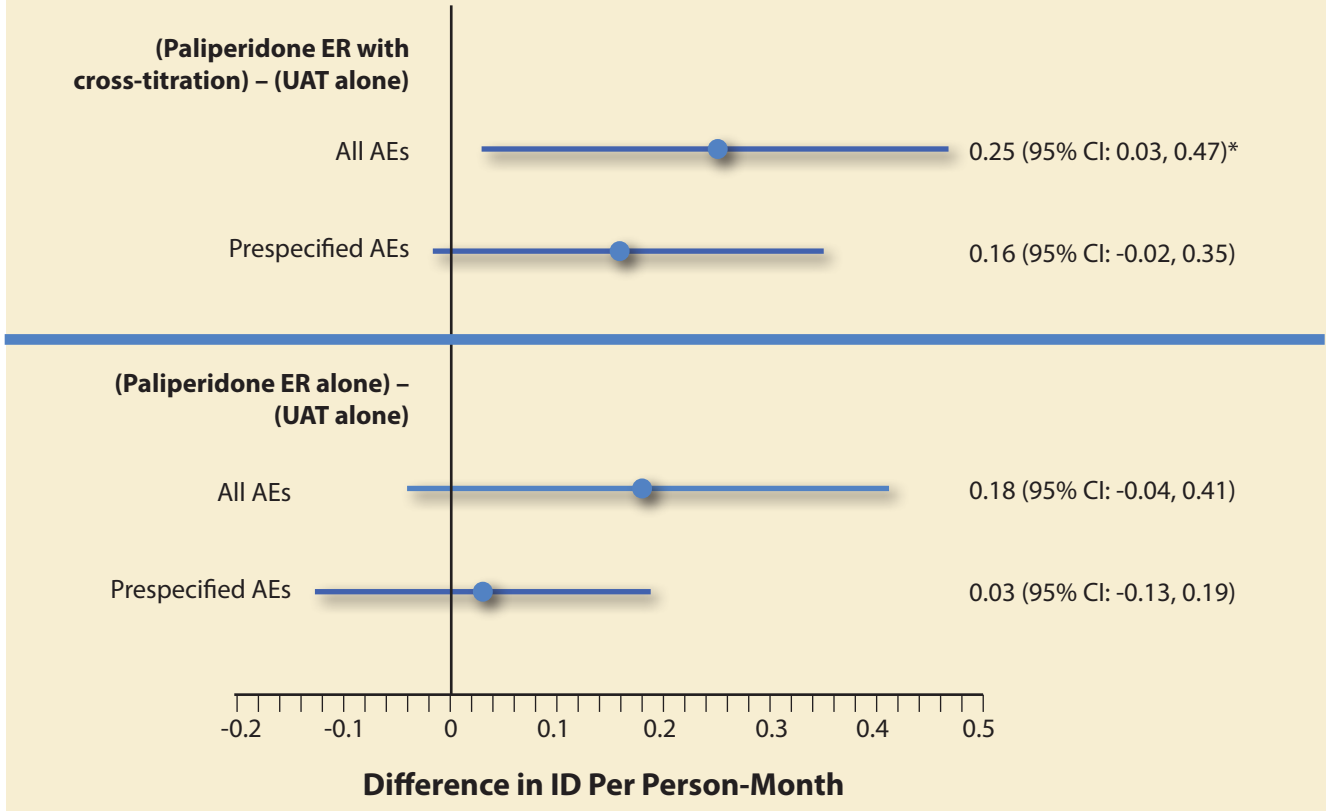
*Of the 85 subjects who completed phase 1, one subject did not meet the criteria to enter phase 2.

Results

Disposition, Baseline Demographics, and Clinical Characteristics

Of the 207 subjects who were screened, 114 (55.1%) entered phase 1 (see Figure 2). Eighty-five subjects (74.6%) completed phase 1; 84 (73.7%) met the criteria to enroll in

Figure 3 Difference in Incidence Density per Person-Month (Safety Analysis Set)



AE=adverse event; CI=confidence interval; ER=extended-release; ID=incidence density; UAT=usual antipsychotic treatment.
*Reached statistical significance.

phase 2 and were included in the safety analysis set. The most common reason for discontinuation during phase 1 (UAT alone) was "other" (11.4%), which included 2 subjects (1.8%) who had unstable hepatic disease, 1 subject (0.9%) who was discontinued at the investigator's discretion, and 10 subjects (8.8%) who were discontinued for other protocol-based exclusion reasons (e.g., failure to meet inclusion criteria for entry into phase 2). The most common reasons for discontinuation in phase 2 were loss to follow-up and withdrawal of consent (each 6.0%).

Overall demographic and baseline characteristics are presented in Table 2. In the safety analysis set, the majority of subjects was male (67.9%) and African American (59.5%) and had a diagnosis of schizophrenia (76.2%). The most common primary etiology of chronic active hepatic disease was viral hepatitis, reported by 83 subjects (98.8%). Based on Child-Pugh criteria, the majority of subjects (76.2%) had well-compensated hepatic disease (class A), and 16.7% had significant functional hepatic compromise (class B). For the majority of subjects in the safety analysis set (73.8%), investigators identified treatment efficacy as the aspect of disease management that could potentially benefit from a change in antipsychotic medication. Of note, 34 (40.5%) subjects in the safety analysis set had previous suicide attempts, and 24 (28.6%) subjects had made more than 1 attempt. Prior substance use was reported by 82.1% of subjects for alcohol, 79.8% for marijuana, 56.0% for cocaine, 31.0% for heroin, 36.9% for stimulants, and 35.7% for depressants (see Table 3).

Table 4 lists the most commonly used (≥5%) concomitant psychotropic medications before the UAT baseline visit, during phases 1 and 2 (for the purposes of this study, UAT also was considered a concomitant medication but was permitted during phase 1 only). The most frequently reported medication was quetiapine, followed by aripiprazole and risperidone. The mean ± SD daily dose of paliperidone ER was 7.4±1.9 mg. The overall mean ± SD study duration was 62.5±6.9 days.

Safety

Adverse Events

The TEAE types reported were similar between both phases (see Table 5). Of the 84 subjects in the safety analysis set, 27 (32.1%) reported ≥1 TEAE during UAT alone, 22 (26.2%) during cross-titration, and 34 (40.5%) during treatment with paliperidone ER alone. Reports of 1 or more of the prespecified AEs were 23 (27.4%) during UAT alone, 20

Table 2 Baseline Characteristics

Parameter	Phase 1 Analysis Set (N=114)	Safety Analysis Set (N=84)
Age, y, mean (SD)	48.1 (7.94)	48.9 (6.73)
Sex, n (%)		
Male	83 (72.8)	57 (67.9)
Female	31 (27.2)	27 (32.1)
Race, n (%)		
White	36 (31.6)	27 (32.1)
Black or African American	70 (61.4)	50 (59.5)
Other	8 (7.0)	7 (8.3)
Primary etiology of chronic hepatic disease, n (%)		
Alcohol	4 (3.5)	0 (0.0)
HBV	1 (0.9)	0 (0.0)
HCV	46 (40.4)	34 (40.5)
Neither HBV nor HCV	2 (1.8)	0 (0.0)
Documented history of viral hepatitis	60 (52.6)	49 (58.3)
Unknown	1 (0.9)	1 (1.2)
Child-Pugh classification, n (%)		
Class A	91 (79.8)	64 (76.2)
Class B	17 (14.9)	14 (16.7)
Missing	6 (5.3)	6 (7.1)
***DSM-IV* diagnosis, n (%)**		
Schizophrenia	86 (75.4)	64 (76.2)
Schizoaffective disorder	28 (24.6)	20 (23.8)
Age at first diagnosis, y, mean (SD)	30.4 (11.7)	31.6 (12.2)
History of suicide attempts, n (%)		
Yes	40 (35.1)	34 (40.5)
No	74 (64.9)	50 (59.5)
Aspects of patient's disease management that could benefit from change in antipsychotic*, n (%)		
Efficacy	85 (74.6)	62 (73.8)
Tolerability	44 (38.6)	33 (39.3)
Adherence	5 (4.4)	2 (2.4)
Comorbid hepatic disease	48 (42.1)	33 (39.3)
Patient and/or family choice	24 (21.1)	18 (21.4)
Convenience/ease of use	8 (7.0)	5 (6.0)
Other	3 (2.6)	2 (2.4)
PANSS total score, mean (SD)	77.0 (12.9)	76.2 (13.4)
CGI-S, n (%)		
Mildly ill	39 (34.2)	33 (39.3)
Moderately ill	52 (45.6)	36 (42.9)
Markedly ill	20 (17.5)	13 (15.5)
Severely ill	3 (2.6)	2 (2.4)
PSP, mean (SD)†	56.2 (12.0)	56.7 (12.0)
MSQ, n (%)†		
Extremely dissatisfied	2 (1.8)	2 (2.4)
Very dissatisfied	11 (9.7)	8 (9.6)
Somewhat dissatisfied	30 (26.5)	23 (27.7)
Neither dissatisfied nor satisfied	18 (15.9)	14 (16.9)
Somewhat satisfied	36 (31.9)	23 (27.7)
Very satisfied	12 (10.6)	9 (10.8)
Extremely satisfied	4 (3.5)	4 (4.8)
SF-36, mean (SD)‡		
Physical health component	42.9 (7.4)	42.3 (7.1)
Mental health component	37.4 (13.3)	36.6 (13.6)

CGI-S=Clinical Global Impressions-Severity; *DSM-IV=Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; HBV=hepatitis B virus; HCV=hepatitis C virus; MSQ=Medication Satisfaction Questionnaire; PANSS=Positive and Negative Syndrome Scale; PSP=Personal and Social Performance; SAS=Simpson-Angus Scale; SD=standard deviation; SF-36=36-Item Short-Form Health Survey; UAT=usual antipsychotic treatment. *Data within categories are not mutually exclusive. †Phase 1 analysis set (n=113); safety analysis set (n=83). ‡Phase 1 analysis set (n=111); safety analysis set (n=82).

Table 3 Substance Use

Substance*	Phase 1 Analysis Set (N=114)	Safety Analysis Set (N=84)
Tobacco, n (%)		
Used	107 (93.9)	78 (92.9)
Never used	7 (6.1)	6 (7.1)
Alcohol, n (%)		
Past use	88 (77.2)	69 (82.1)
Current use	3 (2.6)	2 (2.4)
Past abuse/dependence†	22 (19.3)	15 (17.9)
Never used	10 (8.8)	5 (6.0)
Marijuana, n (%)		
Past use	84 (73.7)	67 (79.8)
Current use	3 (2.6)	1 (1.2)
Past abuse/dependence†	10 (8.8)	6 (7.1)
Never used	24 (21.1)	15 (17.9)
Cocaine, n (%)		
Past use	60 (52.6)	47 (56.0)
Current use	0 (0)	0 (0)
Past abuse/dependence†	18 (15.8)	14 (16.7)
Never used	42 (36.8)	28 (33.3)
Heroin, n (%)		
Past use	32 (28.1)	26 (31.0)
Current use	0 (0)	0 (0)
Past abuse/dependence†	7 (6.1)	6 (7.1)
Never used	77 (67.5)	54 (64.3)
Stimulants, n (%)		
Past use	33 (28.9)	31 (36.9)
Current use	1 (0.9)	0 (0)
Past abuse/dependence†	7 (6.1)	4 (4.8)
Never used	76 (66.7)	51 (60.7)
Depressants, n (%)		
Past use	36 (31.6)	30 (35.7)
Current use	14 (12.3)	11 (13.1)
Past abuse/dependence†	3 (2.6)	2 (2.4)
Never used	62 (54.4)	42 (50.0)

*Data within categories are not mutually exclusive.†Excludes subjects who had a *DSM-IV* diagnosis of substance abuse/dependence or alcohol abuse/dependence in the 6 months before study entry or a urine test result positive for cocaine, opiates (including methadone), or amphetamines at screening.

(23.8%) during cross-titration, and 23 (27.4%) during treatment with paliperidone ER alone. Two subjects in the safety analysis set experienced TEAEs (rash and dystonia) that led to discontinuation from the study; both events occurred during treatment with paliperidone ER alone. The numbers of subjects in the safety analysis set who experienced a serious AE were 0 during UAT alone or during cross-titration and 2 (2.4%; for dystonia and psychotic disorder) during treatment with paliperidone ER alone. No deaths were reported.

Table 4 Concomitant Psychotropic Medications (≥5% in any Group)

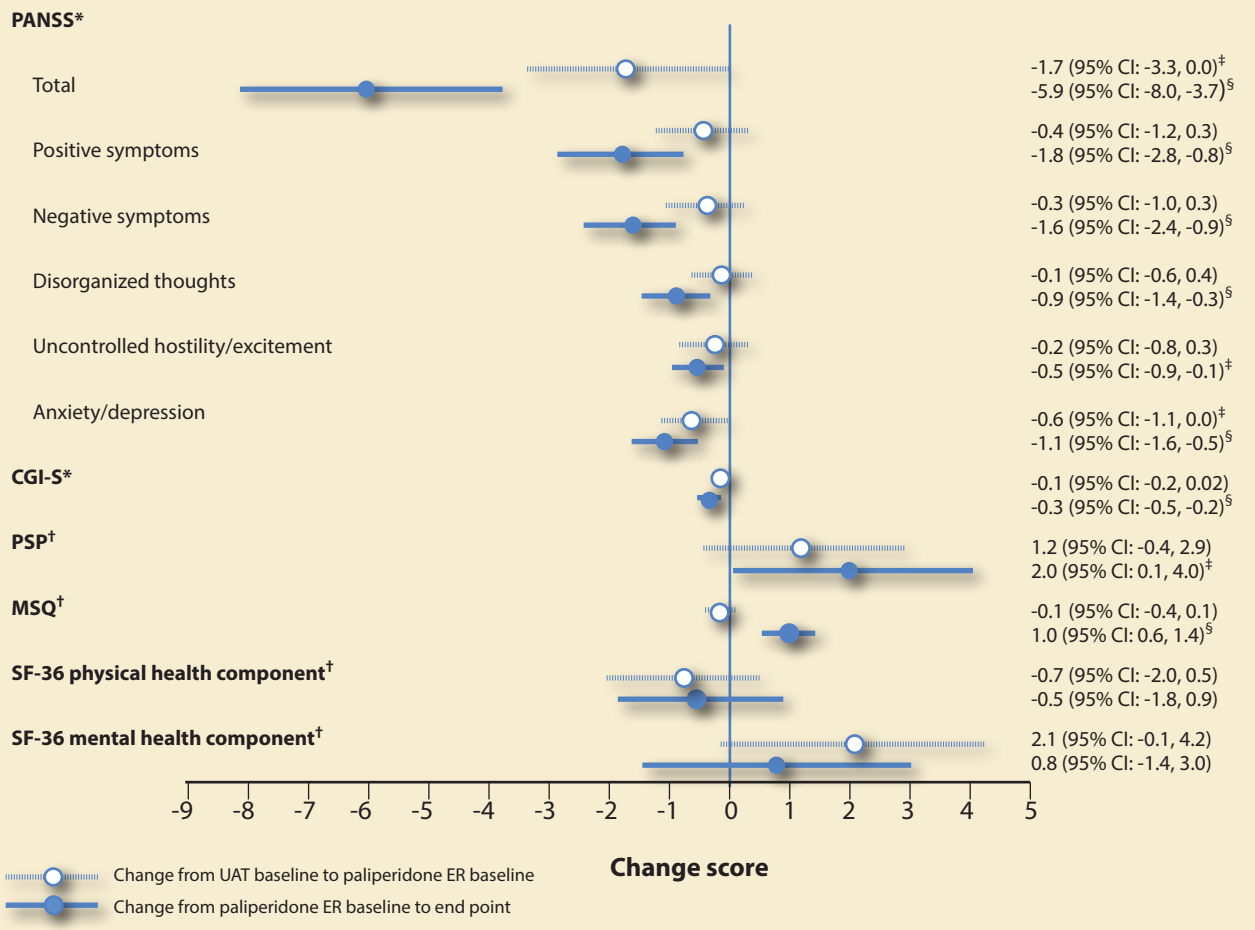
WHO Drug ATC Code/ Preferred Term	Before UAT Baseline Visit (N=114)	During Phase 1* (N=114)	During Phase 2† (N=84)
Antipsychotics, n (%)			
Aripiprazole	24 (21.1)	23 (20.2)	12 (14.3)
Olanzapine	9 (7.9)	9 (7.9)	4 (4.8)
Quetiapine	65 (57.0)	61 (53.5)	42 (50.0)
Risperidone	21 (18.4)	21 (18.4)	13 (15.5)
Ziprasidone	7 (6.1)	7 (6.1)	5 (6.0)
Antidepressants, n (%)			
Mirtazapine	5 (4.4)	5 (4.4)	5 (6.0)
Sertraline	9 (7.9)	9 (7.9)	8 (9.5)
Bupropion hydrochloride	12 (10.5)	11 (9.6)	7 (8.3)
Escitalopram oxalate	6 (5.3)	5 (4.4)	4 (4.8)
Trazodone	14 (12.3)	14 (12.3)	10 (11.9)
Mood stabilizers, n (%)			
Valproate	13 (11.4)	12 (10.5)	6 (7.1)
Sedative/hypnotic, n (%)			
Lorazepam	5 (4.4)	6 (5.3)	7 (8.3)
Other, n (%)			
Benztropine mesylate	15 (13.2)	15 (13.2)	13 (15.5)
Diphenhydramine hydrochloride	4 (3.5)	4 (3.5)	5 (6.0)

ATC=Anatomical Therapeutic Chemical classification; UAT=usual antipsychotic treatment; WHO=World Health Organization.
*Includes all medications that were taken during phase 1, including UAT baseline (visit 2 [day 0]). †Includes all medications that were taken during phase 2, including paliperidone ER baseline (visit 5 [day 27]).

Of the 114 subjects in the phase 1 analysis set, 33 (28.9%) experienced ≥1 TEAE and 24 (21.1%) experienced ≥1 prespecified AE potentially more relevant to antipsychotic treatment. The 2 most commonly occurring TEAEs were also prespecified AEs: weight increase (5 [4.4%]) and headache (3 [2.6%]). Two subjects (1.8%) experienced a serious AE: 1 had a gastrointestinal hemorrhage and 1 had a cerebrovascular accident, both during UAT alone. Four subjects (3.5%) during phase 1 had TEAEs that led to discontinuation from the study: increased blood creatinine level, gastrointestinal hemorrhage, decreased blood potassium level, and cerebrovascular accident.

The ID for all AEs was 0.36 per person-month during UAT alone, 0.61 per person-month during paliperidone ER with cross-titration, and 0.54 per person-month during paliperidone ER alone. Figure 3 shows a statistically significant difference between UAT alone and paliperidone ER with cross-titration (0.25; 95% CI: 0.03, 0.47), but the difference between UAT alone and paliperidone ER alone was not statistically significant (0.18; 95% CI: -0.04, 0.41). The

Figure 4 Change from Baseline for PANSS, CGI-S, PSP, MSQ, and SF-36 Scores (Efficacy Analysis Set)



CGI-S=Clinical Global Impressions-Severity; CI=confidence interval; ER=extended-release; PANSS=Positive and Negative Syndrome Scale; PSP=Personal and Social Performance; SAS=Simpson-Angus Scale; SF-36=36-Item Short-Form Health Survey; UAT=usual antipsychotic treatment. *Negative change represents improvement. †Positive change represents improvement. ‡$p<0.05$. §$p\leq0.002$.

ID for all prespecified AEs was 0.29 per person-month during UAT alone, 0.45 per person-month during paliperidone ER with cross-titration, and 0.33 per person-month during paliperidone ER alone. The difference between UAT alone and paliperidone ER with cross-titration, as well as between UAT alone and paliperidone ER alone, was not statistically significant (see Figure 3). Differences in the cumulative incidences of TEAEs and prespecified TEAEs between these treatment periods were similar. The cumulative incidence of all TEAEs was 0.38 per person-month during UAT alone, 0.77 per person-month during paliperidone ER with cross-titration, and 0.66 per person-month during paliperidone ER alone. The cumulative incidence of the prespecified TEAEs was 0.26 per person-month during UAT alone, 0.49 per person-month during paliperidone ER with cross-titration, and 0.38 per person-month during paliperidone ER alone.

Movement Disorders and Sedation

No significant changes were reported from UAT baseline to paliperidone ER baseline and from paliperidone ER baseline to end point in mean BAS and AIMS scores. There was a significant decrease in mean total SAS score from baseline of UAT to paliperidone ER baseline (-0.2; 95% CI: -0.45, -0.01). However, no significant change was reported from paliperidone ER baseline to end point. No significant changes were observed from UAT baseline to paliperidone ER baseline and from paliperidone ER baseline to end point in the sleep VAS score.

Laboratory Parameters

Laboratory indices, including assessments of LFTs, were consistent with those observed in previous studies of paliperidone ER in subjects without hepatic disease (see Table 6) (27). Similarly, no new safety findings were observed with

Table 5 Treatment-Emergent Adverse Events (≥2% in any Group)

MedDRA System Organ Class Preferred Term, N (%)	Phase 1 Analysis Set (N=114)	Safety Analysis Set (N=84)		
	UAT Alone	UAT Alone	Cross-Titration	Paliperidone ER Alone
Tremor*	2 (1.8)	2 (2.4)	3 (3.6)	4 (4.8)
Headache*	3 (2.6)	3 (3.6)	3 (3.6)	4 (4.8)
Nausea*	1 (0.9)	1 (1.2)	3 (3.6)	2 (2.4)
Insomnia	0 (0)	0 (0)	3 (3.6)	1 (1.2)
Increased weight*	5 (4.4)	5 (6.0)	0 (0)	3 (3.6)
Diarrhea	1 (0.9)	1 (1.2)	2 (2.4)	2 (2.4)
Dry mouth*	1 (0.9)	1 (1.2)	2 (2.4)	1 (1.2)
Increased blood pressure	1 (0.9)	1 (1.2)	1 (1.2)	2 (2.4)
Increased blood prolactin level	1 (0.9)	1 (1.2)	0 (0)	3 (3.6)
Upper respiratory tract infection*	2 (1.8)	2 (2.4)	1 (1.2)	1 (1.2)
Rash*	0 (0)	0 (0)	0 (0)	2 (2.4)
Somnolence*	0 (0)	0 (0)	2 (2.4)	0 (0)
Arthralgia*	2 (1.8)	2 (2.4)	0 (0)	1 (1.2)
Akathisia*	2 (1.8)	2 (2.4)	0 (0)	1 (1.2)

AE=adverse event; ER=extended-release; MedDRA=Medical Dictionary for Regulatory Activities; UAT=usual antipsychotic treatment.
*Prespecified AE.

any other safety parameter (vital sign measurements, physical examinations, and ECG evaluations). In the safety analysis set, no subject had a shift in transaminase values to >3 times the ULN from visit 1 (screening) to visit 4 (day 24). One subject had a shift in AST from 2 to 3 times the ULN to >3 to 4 times the ULN from visit 4 (day 24) to visit 8 (day 62) or end point. In the phase 1 analysis set, 3 subjects had transaminase value shifts to >3 to 4 times the ULN at visit 4 (day 24) and were, therefore, ineligible to continue to phase 2. The mean (SD) change in prolactin levels from screening to day 24 was -0.3 (13.1) ng/mL and from day 24 to study end point was 21.3 (31.1) ng/mL. At day 24, one subject's Child-Pugh classification progressed from well-compensated hepatic disease at baseline (class A) to significant functional hepatic compromise (class B). At day 64, one subject's Child-Pugh classification transitioned from class A at day 24 to class B.

Efficacy

Changes from UAT Baseline to Paliperidone ER Baseline

Small but significant improvements in total PANSS score and the anxiety/depression factor score were observed from UAT baseline to paliperidone ER baseline (p=0.045 and p=0.048, respectively). CGI-S, PSP, and MSQ scores did not change significantly from UAT baseline to paliperidone ER baseline (see Figure 4). There were no statistically significant changes in the physical and mental health components of the SF-36 from UAT baseline to paliperidone ER baseline.

Changes from Paliperidone ER Baseline to Study End Point

For the efficacy analysis set, significant improvements from paliperidone ER baseline to end point were observed in mean total PANSS (-5.9, 95% CI: -8.0, 3.7; p<0.001) and all factor scores (see Figure 4). Mean (SD) CGI-S scores were similar at UAT baseline (3.8 [0.8]) and paliperidone ER baseline (3.8 [0.8]). CGI-S scores significantly improved from paliperidone ER baseline to all subsequent time points (change from paliperidone ER baseline to study end point [-0.3, 95% CI: -0.5, -0.2; p<0.0001]). Similarly, significant improvements in PSP total score (2.0, 95% CI: 0.1, 4.0; p=0.041) and mean MSQ scores (1.0, 95% CI: 0.6, 1.4; p<0.001) were also observed between paliperidone ER baseline and study end point. There were no significant changes for SF-36 from paliperidone ER baseline.

Discussion

As paliperidone ER had not been extensively evaluated in patients with hepatic disease, the purpose of this study was to explore the efficacy and safety of paliperidone ER in patients with schizophrenia or schizoaffective disorder who have mild to moderate hepatic impairment. The emphasis was on rates of spontaneously reported AEs and other safety and efficacy measures relative to UAT. Although exploratory

Table 6 Mean Scores and Change from Baseline for Biochemistry Laboratory Tests (Safety Analysis Set)

Laboratory Test*	Mean (SD)	Change From Screening, Mean (SD)	Change From Paliperidone ER Baseline (Day 24), Mean (SD)
Prolactin (ng/mL)			
Screening (n=82)	11.91 (15.11)		
Day 24 (n=81)	11.82 (11.34)	-0.29 (13.29)	
Day 62 (n=77)	32.50 (31.65)	20.30 (34.72)	21.27 (31.08)
Total bilirubin (mg/dL)			
Screening (n=79)	0.48 (0.21)		
Day 24 (n=80)	0.44 (0.22)	-0.03 (0.14)	
Day 62 (n=73)	0.45 (0.24)	-0.02 (0.15)	0.02 (0.15)
Total protein (g/dL)			
Screening (n=84)	7.66 (0.49)		
Day 24 (n=84)	7.54 (0.52)	-0.12 (0.37)	
Day 62 (n=77)	7.56 (0.56)	-0.09 (0.45)	0.03 (0.51)
Albumin (g/dL)			
Screening (n=84)	4.07 (0.34)		
Day 24 (n=84)	3.95 (0.32)	-0.12 (0.29)	
Day 62 (n=77)	3.97 (0.31)	-0.12 (0.30)	0.01 (0.33)
ALT (SGPT) (U/L)			
Screening (n=84)	38.32 (19.49)		
Day 24 (n=84)	38.88 (22.89)	0.56 (17.22)	
Day 62 (n=77)	40.42 (22.10)	1.22 (17.68)	0.94 (13.04)
AST (SGOT) (U/L)			
Screening (n=83)	35.37 (14.90)		
Day 24 (n=83)	36.29 (18.00)	1.28 (12.80)	
Day 62 (n=76)	36.09 (17.19)	0.44 (14.05)	0.27 (12.77)
GGT (U/L)			
Screening (n=84)	70.36 (70.88)		
Day 24 (n=84)	74.96 (86.45)	4.61 (37.02)	
Day 62 (n=77)	73.31 (81.94)	2.18 (38.12)	0.88 (36.11)
Alkaline phosphatase (U/L)			
Screening (n=84)	84.24 (23.70)		
Day 24 (n=84)	83.60 (24.43)	-0.64 (12.74)	
Day 62 (n=77)	80.49 (24.43)	-2.82 (12.82)	-2.04 (15.87)
Serum sodium (mEq/L)			
Screening (n=84)	140.29 (3.06)		
Day 24 (n=84)	141.21 (4.20)	0.93 (4.03)	
Day 62 (n=77)	140.57 (3.21)	0.25 (3.09)	-0.68 (4.63)
Prothrombin time (sec)			
Screening (n=78)	10.76 (1.33)		
Day 24 (n=82)	10.56 (0.72)	-0.23 (1.39)	
Day 62 (n=72)	10.72 (0.79)	-0.02 (1.47)	0.17 (0.72)

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ER=extended-release; GGT=gamma-glutamyl transferase; SD=standard deviation; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamate pyruvate transaminase; UAT=usual antipsychotic treatment.
*Laboratory tests were conducted during both the UAT (screening and day 24) and the paliperidone ER (day 62) phases.

in nature, this study is, to the best of our knowledge, the largest prospective study to date in this understudied population.

In general, the AE rates reported in this study were lower than might be expected for this particular subpopulation. In the double-blind, placebo-controlled pivotal studies of paliperidone ER in schizophrenia, the pooled AE rate was 72.0% over 6 weeks in patients receiving paliperidone ER 3 to 12 mg (27). The lower AE rate of 40.5% observed in the 4-week paliperidone ER treatment period suggests that paliperidone ER treatment is well tolerated in patients with stable active hepatic disease. Of particular interest is that minimal shifts in LFT values were observed, suggesting that paliperidone ER does not exacerbate hepatic disease.

All TEAEs, including those considered potentially more relevant to antipsychotic treatment, were quantified and analyzed by AE ID and CMF. Although more patients with total TEAEs were reported in the paliperidone ER alone treatment period than in the UAT period, there were no significant differences between the 2 periods in the rates of patients with prespecified AEs. Of note, the IDs for all TEAEs and all prespecified AEs were higher when paliperidone ER was administered during the cross-titration period than when paliperidone ER was administered alone. Indeed, the ID of AEs was greatest during the cross-titration period, and it is well known that many AEs manifest shortly after treatment initiation and subside over time.

In this study, patients with schizophrenia or schizoaffective disorder and hepatic disease, although stable, had a significant degree of psychiatric symptoms and functional impairment at baseline. Patients in this study had particularly high rates of prior substance use, including alcohol, marijuana, cocaine, stimulants, depressants, and heroin. In addition, high rates of previous suicide attempts (35–40%) were observed in this population at baseline, suggesting that these patients may be at particular risk for suicide.

Since risperidone is metabolized by CYP2D6, subjects previously treated with risperidone were included in this analysis. A study of subjects with a suboptimal response to risperidone (28) showed that switching to paliperidone ER demonstrated an improvement in symptoms with no unexpected changes in tolerability. Also, a pooled post hoc analysis of three randomized, placebo-controlled studies showed that paliperidone ER improved symptoms with no unexpected changes in tolerability for patients previously treated with risperidone but who still experienced clinically significant symptoms at study entry (29). These studies suggested that subjects currently treated with risperidone might benefit from paliperidone ER.

Although efficacy evaluation of study medications was limited by the open-label, single-sequence, crossover design, significant improvements in symptoms, severity, and function were consistently observed in PANSS, CGI-S, and PSP scores during the paliperidone ER treatment period compared with those observed at paliperidone ER baseline. Similar benefits were also noted with patient-reported MSQ scores. Changes on these scales during the UAT period were smaller and, for the most part, not statistically significant when compared with the paliperidone ER treatment period. Because investigators identified efficacy as an aspect of patients' disease management that could benefit from a change in therapy, these findings suggest that paliperidone ER may be a useful treatment option in this patient population.

Study limitations include the exploratory, nonrandomized, open-label design and the evaluation of paliperidone ER during and immediately after cross-titration. The lack of randomization and the consistent sequence of treatment (first UAT followed by paliperidone ER) introduced several levels of bias. In the first part of the treatment sequence, all patients stayed on their prior medication. Side effects that may have occurred immediately after beginning those treatments may have subsided or disappeared and may not have been recorded, resulting in potential reduction in observed ID. Dependent censoring may have occurred because the persons who dropped out of phase 1 may have been particularly sensitive to adverse events. None of these subjects was studied in phase 2. Also, discontinuation from stable treatment with UAT may lead to unique stressors, carryover and withdrawal effects that could bias the results against paliperidone ER.

In addition, this trial was of short duration and the long-term safety of paliperidone ER in this population still needs to be confirmed through additional studies. Additionally, as this study was limited to patients with mild to moderate hepatic impairment, the effect of paliperidone ER in patients with severe hepatic impairment, or in patients whose hepatic disease has progressed, could not be established. AEs were determined using spontaneous reporting and not by structured interview, which may have resulted in the underreporting of AEs. However, to further evaluate AEs that typically occur with antipsychotics (EPS and sedation), established scales to measure these conditions were utilized. Further, the prespecified AEs may have excluded AEs considered clinically important, such as dyskinesia, tachycardia, and hyperprolactinemia, which did not meet the definition for this study. As subjects were required to have an aspect of disease management for which change in medication might provide benefit, a selection bias may have occurred in favor of paliperidone ER, where subjects who entered the study because of efficacy or tolerability concerns might be expected to improve those aspects of their disease management through a change in medication. Finally, the study has limited generalizability to a broader population of patients with schizophrenia or schizoaffective disorder and hepatic

disease. Although patients with viral hepatitis or alcoholic cirrhosis were included, the rate of alcoholic cirrhosis observed was lower than expected.

Conclusions

The results of this exploratory, open-label, single-arm, crossover study suggest that paliperidone ER is well tolerated in patients with schizophrenia or schizoaffective disorder who have stable active hepatic disease. No new safety signals were detected in this hepatically compromised patient population. Improvements in psychiatric symptoms and patient functioning were observed after four weeks of treatment with paliperidone ER. A future controlled study with placebo or an active comparator could be conducted to further test the hypothesis that paliperidone ER, with its limited hepatic metabolism, has a favorable risk-benefit profile for patients with schizophrenia or schizoaffective disorder and comorbid hepatic disease.

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