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REVIEW

Paliperidone Palmitate for Schizoaffective Disorder: A Review of the Clinical Evidence

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ABSTRACT

Introduction: Despite being frequently diagnosed, there has been very limited study of efficacious treatments for schizoaffective disorder. Paliperidone had been approved for the treatment of schizoaffective disorder, and a recently completed relapse prevention study of the use of a once-monthly injectable paliperidone formulation has also led to an indication for that preparation to treat schizoaffective disorder.

Methods: To review the efficacy and tolerability of paliperidone for schizoaffective disorder, we conducted a systematic literature search of studies of paliperidone in the treatment of schizoaffective disorder, and briefly reviewed evidence regarding the somewhat controversial nature of that diagnostic entity.

Results: We located several studies of the use of paliperidone extended release in the treatment of schizoaffective disorder, but only one completed study of the use of paliperidone palmitate, which demonstrated efficacy in preventing relapse. Three other studies are currently recruiting participants. Efficacy and tolerability were similar to the profile of oral paliperidone in the treatment of individuals with schizophrenia. These results were similar for both individuals treated with paliperidone palmitate alone, and for those treated with paliperidone palmitate with adjunctive mood stabilizers and/or antidepressants. The use of paliperidone palmitate does not require initial co-administration of oral paliperidone, has relatively little risk of drug–drug interactions, and its pharmacokinetics are favorable for once-monthly administration, an important treatment option for individuals with psychotic disorders, who may often be non-adherent to effective medication regimens.

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Conclusion: Paliperidone palmitate is an approved treatment for schizoaffective disorder, and can be efficacious with or without commonly employed adjunctive treatments.

Keywords: Antipsychotic; Bipolar disorder; Long-acting injectable; Mood disorder; Paliperidone; Paliperidone ER; Paliperidone palmitate; Schizoaffective disorder; Schizophrenia

INTRODUCTION

Schizoaffective Disorder

Schizoaffective disorder has been a controversial diagnosis. It has long been recognized that many patients with psychotic symptoms do not neatly fit into the Kraepelinian diagnostic dichotomy of what we now label schizophrenia and bipolar disorder, but rather present with varying presentations of mood and psychotic symptoms. In 1933, Kasinin proposed the term "schizoaffective psychosis" to designate individuals prominently displaying both psychotic and mood symptoms, claiming that those so diagnosed would have a better prognosis [1].

The "affective" portion of the term "schizoaffective" itself remains something of an anachronistic misnomer, as aside from the psychotic symptomatology, there is also a primary disturbance in mood (a pervasive and sustained emotional state), not affect per se. Affect is defined as observable behaviors that express a current emotional state, which may fluctuate; in the past, other mood disorders were also inaccurately labeled "affective" disorders.

Early versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM) included this entity using slightly different terminology, such as "schizophrenic reaction, schizoaffective type" in DSM-I and "schizophrenia, schizoaffective type" (either excited or depressed) in DSM-II, but in 1980 in DSM-III it was named "schizoaffective disorder," and was the only diagnosis in that edition that did not employ specific diagnostic criteria. In DSM-III-R (1987) criteria were introduced, which required a period of psychosis meeting criteria for schizophrenia during which mood symptoms were present for "more than a brief" period of time, and also a period of psychotic symptoms without mood symptoms of at least two weeks, to distinguish schizoaffective disorder from a mood disorder with psychotic symptoms. DSM-IV (1994) further recognized two subtypes of schizoaffective disorder: "depressive type" and "bipolar type," and DSM-IV-TR (2000) required that the mood symptoms must be present for "a substantial portion" of the course of the disorder, without further quantification.

This vagueness in the diagnostic criteria has been further compounded by the common difficulty in obtaining an accurate longitudinal description of the course of patients' symptoms. It is commonly not possible to adequately establish accurate periods of time for which prominent mood symptoms have been present over the course of a patient's history with and without delusions and hallucinations, and verify that such symptoms were not caused by the use of, or withdrawal from, substances of abuse, let alone formally decide on the definition of "substantial period." Not surprisingly, therefore, kappa values for diagnostic agreement have been notably poor: Hiller et al. [2] reported a kappa of 0.08 using DSM-III-R criteria for schizoaffective disorder, and Maj et al. [3] reported a kappa of 0.22 using DSM-IV criteria, far below the more desirable

range indicating at least moderate interrater agreement (0.4–0.6).

Appreciably better kappa values have been reported using International Classification of Diseases (ICD)-10 criteria, although that criteria set is quite similar to that of DSM-IV-TR. However, a study in Denmark of patients with hospital discharge diagnoses of schizoaffective disorder found that none met DSM-IV-TR criteria and only 10% met ICD-10 criteria [4]. Seeking to improve reliability, DSM-5 (2013) usefully added the specification that the symptoms of a major mood episode were present for the majority of the total duration of the active and residual portions of the illness, which is somewhat more specific, although whether this will appreciably improve diagnostic reliability and validity must await future study [5]. Exploring issues regarding the validity of the diagnosis, a detailed review by Kantrowitz and Citrome [6] examined possible differentiating characteristics that would distinguish schizoaffective disorder from schizophrenia and bipolar disorder, including prognosis, genetic linkage studies, neuropsychological testing and pharmacological response, finding at best very modest evidence, although some results of neurophysiological sensory testing pointed towards some possible discriminating characteristics. Likewise, a longitudinal study of first-admission patients with a diagnosis of schizoaffective disorder did not generate support for the validity of the diagnosis of schizoaffective disorder based on symptom course and outcomes [7].

In fairness, however, it should be noted that schizophrenia and bipolar disorder themselves do not admit of neatly separating genetic findings, with not only numerous proposed genetic linkages, but with some that appear to be common for both schizophrenia and psychotic bipolar disorder [8]. Moreover, there have been thoughtful proposals to formulate schizophrenia, schizoaffective disorder and bipolar disorder as representing more of a continuous spectrum, or viewed in a dimensional approach [9]. Clearly, this is still an enduring area of controversy; it remains a significant nosologic challenge for the field's attempts to skillfully "carve Nature at its joints".

Given these concerns, one must explain why we have the diagnostic category of schizoaffective disorder. Of most relevance is the fact that this diagnosis is very commonly used, with an estimated lifetime prevalence of 0.3% [10], that is, a third or more as common as the diagnosis of schizophrenia, and translating to about 750,000 adult Americans. It likely serves as a useful clinical marker for the clinician to consider the adjunctive use of mood stabilizers or antidepressants in a given patient, which indeed is commonly done, although there is little high-quality evidence available supporting the efficacy of these adjunctive treatments. Notably, in 2009, the Food and Drug Administration (FDA) approved paliperidone for the treatment of schizoaffective disorder, the first time that the agency recognized this as a valid diagnostic entity for a therapeutic indication [11]. Since that time, when new antipsychotic agents have been submitted for approval using studies that enroll both individuals with schizophrenia and schizoaffective disorder, the FDA has examined data for those two diagnostic groups separately. Recently, the FDA expanded the indication for paliperidone, to include relapse prevention of schizoaffective disorder using a long-acting injectable (LAI) formulation of paliperidone, paliperidone palmitate [12].

Paliperidone

Paliperidone (trade name Invega®; Janssen), the 9-hydroxy active metabolite of risperidone (trade name Risperdal®; Janssen) responsible for most of the antipsychotic potency of risperidone, is an antipsychotic medication that was developed by Janssen Pharmaceuticals, and was approved by the FDA in 2006 for the indication of the treatment of schizophrenia [11]. It is available in an oral extended-release formulation (paliperidone ER) that employs two drug layers and an osmotically active core layer that pushes the drug out ("OROS," a patented technology), allowing for slow, more even drug release supporting convenient once-daily dosing. Like other second-generation antipsychotics, it is believed that paliperidone's antipsychotic mechanism of action is antagonism at dopamine D2 receptors and serotonin-2A receptors in the brain, the latter action also helping limit some extrapyramidal adverse effects. Paliperidone is also an antagonist at α_1 and α_2 adrenergic and H_1 histamine receptors, but, unlike most first-generation antipsychotics, not at muscarinic cholinergic receptors [13].

Activity at particular receptors informs expectations for specific adverse effects. Specifically, blocking dopamine D2 receptors does dampen down agitation and helps treat delusions and hallucinations, but, if too pronounced, may result in the extrapyramidal side effects of dystonic reactions, parkinsonism, and tardive dyskinesia, as well as akathisia (pronounced restlessness in the lower extremities), and may cause neuroleptic malignant syndrome. D2 receptor antagonism also increases serum prolactin levels, which may interfere with the menstrual cycle or cause lactation in women, and may cause breast swelling and interfere with sex drive and functioning in either sex, with long-term use potentially decreasing bone density. Blocking serotonin-2A receptors may help with anxiety, irritability, insomnia, and mitigate some extrapyramidal side effects. Alpha$_1$-adrenergic blocking medications such as prazosin and doxazosin have use in treating hypertension and benign prostatic hypertrophy, but are also prescribed off-label in treating posttraumatic stress disorder; they may be associated with adverse effects of postural hypotension and nasal congestion, as well as priapism and retrograde ejaculation [14, 15]. Alpha$_2$-blocking medications such as clonidine and guanfacine have been used to treat attention-deficit disorder symptoms, and may be associated with dry mouth, sedation, dizziness and constipation. Histamine H_1 antagonists treat allergies, but also can cause sedation and weight gain. As with many other antipsychotic medications, an increase in weight may be associated with glucose intolerance and the development of diabetes mellitus or a metabolic syndrome.

Knowledge of these other receptor effects is useful in treating individuals who often have co-occurring symptoms or disorders, or heightened sensitivities to particular adverse effects. Paliperidone does modestly increase the electrocardiogram QT interval, an issue for individuals particularly vulnerable to this effect, and can make certain medication combinations (such as with citalopram) problematic.

Paliperidone ER (available in 1.5, 3, 6 and 9 mg extended-release tablets) is the marketed oral formulation, and has a maximum serum concentration (C_{max}) approximately 24 h after a single dose. It can be taken with or without food, but it should be noted that it has 28% absolute oral bioavailability, with area under the plasma drug concentration–time curve

(AUC) increased by 54% when administered with a standard high-fat/high-caloric meal. The recommended dose of the tablet is 6 mg/day (once-daily dosing), with a maximum recommended daily dose of 12 mg/day; pharmacokinetics are dose-proportional within the recommended dose range [11].

The long-acting parenteral form, paliperidone palmitate, is available in 39, 78, 117, 156 or 234 mg doses of injectable suspension (providing paliperidone doses equivalent to 25, 50, 75, 100 and 150 mg, respectively). Individuals should have had some previous exposure to either risperidone or paliperidone to rule out any severe intolerance, before beginning long-acting parenteral treatment. The recommended initial dosing to treat schizophrenia or schizoaffective disorder is administering 234 mg on the first day and 156 mg one week later, both in the deltoid muscle to facilitate more rapid absorption (and therefore not require a lead-in period of oral supplementation). Following this, an appropriate intramuscular dose should be administered monthly afterwards, in the deltoid or gluteal muscle, as preferred, of 39, 78, 156 or 234 mg (the 39 mg monthly dose was not studied in patients with schizoaffective disorder).

Paliperidone is metabolized by CYP2D6 and CYP3A4, but only to a limited extent, and is mainly excreted renally. Following a single oral dose, 59% was excreted unchanged in the urine, and most of the metabolites were also renally excreted. Because of limited hepatic metabolism, mild or moderate hepatic impairment has little effect on dosing recommendations, and extensive or poor metabolizer status for CYP2D6 is not particularly important, although the dose should be lowered for those with renal impairment. Dosage adjustment upwards of paliperidone may be required in the presence of strong CYP3A4/P-glycoprotein inducers (for example, carbamazepine, rifampin, St. John's wort).

Paliperidone does not substantially inhibit the CYP450 hepatic enzymes, and is a weak inhibitor of P-glycoprotein but only at high concentrations; it is therefore also not likely to significantly affect the metabolism of other drugs.

METHODS

This article does not contain any new studies with human or animal subjects performed by any of the authors. The analysis in this article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

Searches were conducted on March 13, 2015 of PubMed, Embase, and Web of Science using the text words "paliperidone" and "schizoaffective", and ClinicalTrials.gov using "paliperidone palmitate". Both authors reviewed the results of the searches for relevance. These searches identified the one published pivotal relapse prevention study. Additionally, one brief case report was identified regarding the combined use of paliperidone palmitate and olanzapine pamoate in treatment-resistant schizoaffective disorder [16]. Another abstract briefly addressed the subsequently published full report of the relapse prevention trial. For added context, we also reviewed some key studies of paliperidone ER in the treatment of schizoaffective disorder.

EFFICACY OF PALIPERIDONE FOR SCHIZOAFFECTIVE DISORDER

Acute Studies

There have been two acute clinical trials of the oral formulation paliperidone ER for

schizoaffective disorder [17, 18]. A pooled analysis of these two 6-week registration trials of paliperidone ER for the acute treatment of individuals aged 18–65 years with schizoaffective disorder diagnosed using the Structured Clinical Interview for DSM-IV Disorders (SCID) included 614 subjects in the intent-to-treat population; 414 were randomized to receive paliperidone ER 3–12 mg/day and 200 to receive placebo [19]. Of these, 275 (45%) of subjects had been receiving adjunctive treatment with mood stabilizers and/or antidepressants; these adjunctive medications were continued for both treatment groups. All enrolled subjects were experiencing an acute exacerbation of their psychotic disorder at screening; had a Positive and Negative Syndrome Scale (PANSS) score $\geq$60 with a score $\geq$4 on two or more of the PANSS items hostility, excitement, tension, uncooperativeness and poor impulsive control; had significant mood symptoms as evidenced by a score $\geq$16 on the Young Mania Rating Scale (YMRS) and/or a score $\geq$16 on the Hamilton Rating Scale for Depression, 21-item (HAM-D-21).

In one study (ClinicalTrials.gov identifier, NCT00397033), subjects receiving paliperidone were randomized to receive 9–12 mg of paliperidone/day or 3–6 mg of paliperidone/day (dosed at the higher number, and later reduced if clinically indicated) [17]. In the other study (ClinicalTrials.gov identifier, NCT00412373), those randomized to paliperidone received 6 mg/day to start, but were then flexibly dosed, as clinically appropriate, in the range of 3–12 mg/day [18]. Both studies stratified randomization by study center and by whether the subject was being concurrently treated with mood stabilizers and/or antidepressants. The primary efficacy outcome measure for both studies was the change in the PANSS total score from baseline to endpoint, and secondary efficacy measures included changes in the Clinical Global Impressions of Severity for Schizoaffective Disorder (CGI-S-SCA), PANSS factor scores, YMRS, and HAM-D-21 scores [20].

Demographic and clinical characteristics at baseline were similar for the treatment groups. Overall, 275 subjects were taking mood stabilizers and/or antidepressants; 69% of this group were taking mood stabilizers (principally valproate) and 59% were taking antidepressants. Subjects randomized to paliperidone ER improved significantly more from day 4 to study endpoint, the placebo-adjusted least square mean (SE) difference at last observation carried forward (LOCF) for the PANSS total score was -7.8 (1.7), with $P < 0.001$, and an effect size of 0.41; both subgroups with and without adjunctive mood stabilizer/antidepressant adjunctive treatment improved significantly more with paliperidone compared with placebo treatment. Secondary measures all were significantly better for the paliperidone treatment group as well, compared with placebo.

Maintenance (Prevention of Relapse)

A randomized, double-blind, placebo-controlled study with a 15-month relapse prevention phase examined the efficacy of monthly intramuscular injections of paliperidone palmitate compared with placebo during that phase (ClinicalTrials.gov identifier, NCT011193153) [21]. As in the acute studies of paliperidone, enrollees were diagnosed with schizoaffective disorder using the SCID interview (DSM-IV, Clinician Version), and were stratified by study center and by subjects' concurrent use of mood stabilizers or antidepressants or the lack of such treatment, and by study center in this

international study. Those who had received treatment with both mood stabilizers and antidepressants were excluded from study participation (this was not a criterion in the previous acute study), as were individuals who had begun treatment with mood stabilizers or antidepressants or had dosage changes in the 30 days prior to screening. Pre-study treatment with benzodiazepines was also allowed to continue at a stable dose, and there was some limited allowance for newly initiating benzodiazepines or other hypnotics during the study.

Enrolled subjects were required to be experiencing an acute exacerbation of psychotic symptoms at screening, as evidenced by a score $\geq$4 on 3 or more of the PANSS items: delusions, conceptual disorganization, hallucinatory behavior, excitement, suspiciousness/persecution, hostility, tension, uncooperativeness, and poor impulse control, and were experiencing significant mood symptoms, as evidenced by a YMRS and/or HAM-D-21 score $\geq$16. After enrollment, subjects began a 13-week open-label lead-in phase during which all received the two recommended initial doses of paliperidone 1 week apart (234 mg on Day 1, 156 mg on Day 8) and then flexible-dose intramuscular paliperidone palmitate monthly (78–234 mg), followed by a 12-week stabilization phase during which treatment continued with the established dose for each subject. No oral supplementation of antipsychotics was permitted in this study. Stabilization criteria included a PANSS total score $\leq$70, and YMRS and HAM-D-21 scores $\leq$12.

Those continuing were randomized to receive either monthly injections of paliperidone palmitate or placebo during the 15-month double-blind relapse prevention phase. Subjects were considered to have relapsed if they met any 1 or more of the following conditions: psychiatric hospitalization due to worsening of symptoms; other significant interventions exercised to avoid hospitalization for worsened symptoms such as increasing the level of care or adding additional medications; clinically significant self-injury or violent behavior or suicidal or homicidal ideation; significant worsening on any of several key PANSS or on several other PANSS measures, or on the CGI-S-SCA. The primary efficacy outcome measure was the comparison of relapse risk for psychotic and/or mood symptoms while treated with paliperidone palmitate, compared with placebo; a key secondary objective was comparison of the subject functional status, as measured by the Personal and Social Performance scale (PSP) [22].

There were 667 subjects who enrolled and received at least one dose of medication in the open-label phase; 334 were randomized 1:1 in the double-blind phase to paliperidone palmitate or placebo injections. In the double-blind period, the most commonly used dose of paliperidone palmitate was 156 mg (47.0%), followed by 234 mg (38.4%), 117 mg (9.8%), and 78 mg (4.9%). 15.2% of those randomized to paliperidone palmitate relapsed, as compared with 33.5% of those receiving placebo (hazard ratio 2.49 times greater for placebo, 95% confidence interval 1.55–3.99, $P < 0.001$; number needed to treat 6). For those receiving adjunctive mood stabilizers or antidepressants, the relapse risk was 2.03 times for those on placebo compared with paliperidone; for those not receiving adjunctive mood stabilizers or antidepressants, the relapse risk was 3.38 times for those on placebo compared with paliperidone. Overall, paliperidone palmitate was superior to placebo in maintaining functioning measured by the PSP scale

($P = 0.014$, mixed-model repeated measures). Significant improvements were also found at study endpoint for HAM-D-21, YMRS, PANSS, and CGI-S-SCA total scores for the paliperidone group, compared with the placebo group.

TOLERABILITY OF PALIPERIDONE FOR SCHIZOAFFECTIVE DISORDER

Tolerability of Paliperidone ER for Schizoaffective Disorder

The most common adverse events reported in subjects in the paliperidone ER for schizoaffective disorder registration trials (≥5.0% and 2× placebo) were tremor (8.1% vs. 3.5% with placebo, number needed to harm [NNH] 22), hypertonia (5.5% vs. 2.0% with placebo, NNH 29), dyspepsia (5.5% vs. 2.5% with placebo, NNH 34), and somnolence (5.2% vs. 2.0% with placebo, NNH 32). For both paliperidone ER and placebo treatment groups, 7% of subjects discontinued treatment due to adverse events. For both males and females, treatment with paliperidone ER was associated with increases in serum prolactin levels.

Tolerability and Safety of Paliperidone Palmitate for Schizoaffective Disorder

Interpreting differences in tolerability outcomes versus placebo in the randomized phase is complicated because subjects with tolerability problems may have dropped out during the prior open-label treatment phase. In the paliperidone palmitate relapse prevention study, 28.2% of the placebo group discontinued treatment during the double-blind phase, compared with 23.8% of those in the paliperidone group. Higher rates of subjects discontinued because of withdrawal of consent and being lost to follow-up in the control groups, but 5.5% of subjects in the paliperidone group discontinued due to an adverse event, as opposed to 1.8% on placebo (NNH 27). There were 2 deaths in the paliperidone group during the double-blind phase, as well, one by overdose of sleeping medication and one due to coronary artery disease, neither judged by the investigator as caused by the investigational product.

The common (≥5%) treatment-emergent adverse events (TEAEs) reported more frequently in the paliperidone group than in the placebo group were: weight increased (8.5% paliperidone, 4.7% placebo, NNH 27), nasopharyngitis (5.5% paliperidone, 3.5% placebo, NNH 50), and headache (5.5% paliperidone, 3.5% placebo, NNH 50). Extrapyramidal symptom-related TEAEs were reported in 8.5% of the paliperidone group, compared with 7.1% of the placebo group (NNH 72). Prolactin-related TEAEs occurred in 13.9% of women in the paliperidone group, compared with 5.8% of women in the placebo group (NNH 13). Thirteen percent of paliperidone-treated compared with only 6% of placebo-treated subjects gained ≥7% of their weight during the study (NNH 15), although there was only minimal mean weight change reported for both groups.

PLACE IN THERAPY: AN OVERVIEW OF OTHER TREATMENTS COMMONLY USED TO TREAT SA DISORDER

Paliperidone palmitate has joined the limited ranks of LAI antipsychotic formulations available. In the US, other available alternatives include fluphenazine decanoate, haloperidol decanoate, aripiprazole (trade

name Abilify Maintena®; Otsuka Pharmaceutical Company), risperidone (trade name Risperdal Consta®; Janssen) and olanzapine pamoate (trade name Zyprexa Relprevv®; Eli Lilly and Company); other options are available outside of the US. These other LAIs do not have a specific indication for schizoaffective disorder, although in clinical practice they are commonly used for this indication, and it would appear likely that antipsychotics effective for schizophrenia would generally be effective for schizoaffective disorder. Fluphenazine and haloperidol are first-generation antipsychotics, and although they are much less expensive, may be more prone to cause extrapyramidal side effects.

Of the second-generation antipsychotics, risperidone appears somewhat more likely to cause extrapyramidal side effects, and its pharmacokinetic properties are not conducive to monthly maintenance injections for most; it also requires a period of initial oral supplementation. Olanzapine pamoate has been associated with severe sedation as a rare but serious adverse reaction (post-injection delirium sedation syndrome), and patients must be observed for at least three hours after injections in a registered facility with ready access to emergency services [23]. One US multisite, double-blind randomized head-to-head comparison of haloperidol decanoate to paliperidone palmitate in the maintenance treatment of patients diagnosed with schizophrenia or schizoaffective disorder found no significant difference in the rate of efficacy failure, and on the safety side reported more weight gain and increased prolactin levels in those on paliperidone palmitate, and more akathisia in patients taking haloperidol decanoate [24]. Aripiprazole, a D2 partial agonist, is also available as a long-acting injection, and an application of a formulation from a different manufacturer is currently under FDA review [25].

The issue of acquisition cost is a significant one, as access to the much more expensive, branded drugs is being affected by their needing to be reviewed for prior authorization by most pharmacy benefit managers. Of note is the recently published clinical trial of a new three-month formulation of paliperidone palmitate [trade name Invega Trinza®], used successfully to prevent relapse in subjects with schizophrenia, which the FDA has recently approved for this indication. (ClinicalTrials.gov identifier, NCT01529515) [26, 27]. A three-month LAI formulation is a very welcome therapeutic option for non-adherent patients and their families and treatment providers. Choosing an appropriate LAI involves a number of pertinent considerations, including knowledge of the particular pharmacokinetics of the relevant options and likely adverse events [28]. Guidance regarding how to best switch antipsychotic medications has received only limited attention, particularly for schizoaffective disorder [29].

SUMMARY AND CONCLUSIONS: BALANCING EFFICACY AND SAFETY

Paliperidone appears to be an effective modality not only in the acute treatment of schizoaffective disorder, but in preventing relapse for those with this disorder, the latter as evidenced in a 15-month maintenance of effect trial of paliperidone palmitate as both a monotherapy and as adjunct to oral mood stabilizers or antidepressant medication. Paliperidone is generally tolerated well, although its propensity to increase prolactin levels and cause extrapyramidal side effects and

weight gain should be recognized. It can be used with adjunctive mood stabilizers or antidepressants, if they appear indicated. Favorable characteristics include its not requiring an initial oral supplementation period because of favorable pharmacokinetic parameters, and not being significantly affected by drug–drug interactions or CYP450 hepatic enzyme poor- or rapid-metabolizer status, decided advantages for some patients, although dosage adjustments may be needed for those with poor renal function. If the three-month version is also effective for those with schizoaffective disorder, this will prove a considerable benefit in treating non-adherent individuals or those who elect to receive a medication 4 times a year for convenience.

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Compliance with ethics guidelines. This article does not contain any new studies with human or animal subjects performed by any of the authors. The analysis in this article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

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