Comment

Pharmacology

Pharmacology 2019;104:67–70
DOI: 10.1159/000500629

Received: March 12, 2019
Accepted: April 25, 2019
Published online: May 16, 2019

Paliperidone Use in Child Psychiatry: Evidence or Diffidence?

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Keywords
Paliperidone · Child psychiatry · Pharmacology · Clinical uses

Abstract
Background: Paliperidone is FDA-approved for schizophrenia aged 12–17. However, the pharmacologic portfolio, extrapolation from adult studies, and the long track record of the parent drug, risperidone in child/adolescent psychiatric (CAP) population might expand its therapeutic potential. ***Methods:*** EMBASE, Ovid MEDLINE, PubMed, Scopus, Web of Science, and Cochrane Database of Systemic Reviews were searched for all relevant studies of using paliperidone in child psychiatry up to date of February 2019. ***Results:*** Sound evidence base supports its use in early-onset schizophrenia, juvenile bipolar, and autism spectrum disorder. A modicum of evidence supports its use in Tourette syndrome and as adjuventia in attention-deficit/hyperactivity disorder (ADHD). ***Conclusion:*** Paliperidone has some dynamic and kinetic superiority to the parent drug risperidone. Nonetheless, larger rigorous studies would define the real place of the atypical antipsychotic paliperidone in child and adolescent psychiatry. Until then, risperidone with its long track record in CAP population would remain a first option though.

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Introduction

Paliperidone is FDA-approved for schizophrenia aged 12–17. However, pharmacologic portfolio, downextension from adult studies, and the long track record of use of the parent drug, risperidone in child/adolescent psychiatric (CAP) population might expand its therapeutic potential in this population. Here, we shed some light on the pharmacology of paliperidone followed by a discussion of such off-label indications while examining the extant evidence from literature. Use of paliperidone palmitate, the long-acting injectable antipsychotic (LAIA) form, would be briefly discussed as germane to CAP population.

These uses include inter alia, juvenile bipolar mood disorder, disruptive behavioral disorders, autism spectrum disorder (ASD), and Tourette syndrome (TS).

Paliperidone Pharmacology

Paliperidone [1], 9-hydroxyrisperidone, is an atypical antipsychotic, a serotonin ($5HT2_A$) dopamine (D2) antagonist and the active metabolite of the high-potency risperidone. It has also 5HT7 antagonism that might confer some antidepressant actions. It is advantageous given the osmotic-controlled release oral delivery system technique facilitating once-daily dosing, rapid

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steady-state, and hence better compliance. Moreover, lack of cytochrome CYP-450 enzyme interactions, more alpha-2 affinity, alleged less propensity for extrapyramidal syndromes, and availability of long-acting injection formulation all render paliperidone a very appealing treatment option in psychoses and in hepatic patients too. Amatniek et al. [2] have conducted a multicenter, open-label, single-arm, crossover study evaluating the safety and efficacy of paliperidone-extended release (ER) in patients with schizophrenia or schizoaffective disorder and hepatic disease and shown that paliperidone was well tolerated in this subpopulation. It has a half-life of 23 h. In adolescent clinical trials, systematic exposure was similar to that in adults. It is taken regardless to food; absorption might be reduced if taken on empty stomach, though. For those weighing <51 kg, it is dosed in range of 3–6 mg/day OD or BID and titrated q 5 days. For those >51 kg, it is dosed in the range of 3–12 mg/day.

Along with risperidone, it causes the most extrapyramidal syndromes and hyperprolactinemia of all the second-generation antipsychotics. Gopal et al. [3], in a post hoc analysis of a 2-year open-label multicenter study, assessed potentially prolactin-related treatment-emergent adverse events (PPRL-TEAEs) and sexual maturation during long-term treatment of adolescents with paliperidone ER. Female sex, age at diagnosis (13–14 years), girls of Hispanic ethnicity, and region (EU and North America) were associated with a greater risk for PPRL-TEAEs; higher baseline Tanner stages for pubic hair (boys and girls) and breast development (stage 3 vs. 4 or 5) also seemed to be associated with a higher incidence of PPRL-TEAEs.

It might cause more QTc prolongation than risperidone as shown by Suzuki et al. [4].

Paliperidone in CAP Population

A retrospective chart-review study by Yektas et al. [5] investigating the use of paliperidone in various psychiatric disorders in CAP population have shown the mean age of patients was 15.8 ± 1.3 years, with 59.6% (n = 31) of the group was male and 40.4% (n = 21) was female. Paliperidone was prescribed for median 150 days. The median average daily dose was 7.6 mg/day (range 3–12 mg/day). The main indications for paliperidone prescription were psychotic disorders and bipolar disorders (17 patients, 32.6%; 16 patients, 30.7%, respectively). The other most common diagnostic group was disruptive behavior disorders (DBDs) associated with attention-deficit hyperactivity disorder (ADHD), ASDs, intellectual disability, conduct disorders, or oppositional defiant disorders (15 patients; 28.8%) tic/neurological disorder (4 patients; 7.9%). Thirty-five patients (67.4%) did not have a diagnosis of schizophrenia and were considered to have received these drugs off-label. Dosing was notably lower in the group of DBDs patients than for patients with bipolar disorder or psychotic disorders. Of the 52 patients receiving paliperidone, 53.9% of patients were concurrently treated at some point with one or more psychotropic agents. Totally, adverse drug reactions were recorded in 26 (50%) patients: weight gain (n = 24), extra pyramidal symptoms (n = 8), and hyperprolactinemia (n = 4).

Similarly, De Cos Milas et al. [6] described their clinical experience with paliperidone in adolescents. They presented 3 males and 2 females, age between 15 and 17 years. Diagnoses were autism, borderline personality disorder, schizotypal personality disorder, personality disorder not otherwise specified, and schizophrenia. Prescribed dose was 3–9 mg/day, and actual mean time of treatment duration is 5.8 months. In 4 cases, paliperidone was initiated as a change from other antipsychotic. There were no adverse effects that required discontinuation and in all cases symptoms improved.

Methods

EMBASE, Ovid MEDLINE, PubMed, Scopus, Web of Science, and Cochrane Database of Systemic Reviews were searched for all relevant studies of using paliperidone in child psychiatry up to date of February 2019.

Schizophrenia

Paliperidone is currently approved for those aged 12 with schizophrenia based on a positive RCT by Singh et al. [7]. In this 6-week, double-blind, parallel-group study of 201 participants ages 12–17 years, 3 weight-based fixed doses of paliperidone ER were compared to placebo. Only the medium (3–6 mg) treatment resulted in a statistically significant improvement. As such, it was concluded that there was no need for weight-based dosing. Moreover, Savitz et al. [8] compared paliperidone ER and aripiprazole in randomized, double-blind, parallel groups and found no difference between groups.

Bipolar Mood Disorder

An 8-week open-label study [9] examined paliperidone monotherapy for acute mania, mixed, or hypomanic episode in pediatric patients (n = 15, 6–17 years of age) with bipolar spectrum disorders. At the end of follow-up period, 11 subjects (73%) completed the study; treatment with paliperidone was associated with a 60% response rate (50% decrease in the Young Mania Rating Scale) and 40% remission (YMRS <12)

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Autism Spectrum Disorder

Stigler et al. [10] evaluated the effectiveness and tolerability of paliperidone for irritability in ASD. In this 8-week, prospective, open-label study, 21 (84%) of 25 subjects with ASD (mean age, 15.3 years) were considered responders to paliperidone (mean dosage, 7.1 mg/day), based on Clinical Global Impression (CGI)-Improvement and Aberrant Behaviour Checklist-Irritability subscale.

In the same vein, Kowalski et al. [11] have reported on the successful use of paliperidone palmitate for the treatment of severe irritability in a 5-year-old child with autism who was unable to tolerate oral medications.

Attention-Deficit Hyperactivity Disorder

Fernandez-Mayoralas et al. [12] have conducted a prospective 16-week open-label study of paliperidone in 18 patients (mean age, 13.4 years) with severe and excessive irritability in the context of generalized developmental disorders or ADHD. Patients who had exhibited an inadequate response to treatment with risperidone (1.5–2 mg/day) over a treatment period of 6 months were treated with paliperidone at 3 mg/day. Symptom severity at the beginning of the study and in response to paliperidone wsa rated with the CGI scale and Overt Aggression Scale. A significant difference was documented between the mean score before treatment and the score after the drug intervention with paliperidone. There was a noticeable clinical improvement in 50% of the cases, as reflected in the CGI. Severity of aggressive behavior, as assessed by the Overt Aggression Scale, decreased significantly after paliperidone treatment. paliperidone was safe and well tolerated.

Tourette's Syndrome

Yamamuro et al. [13] have reported on 3 CAP cases with TS treated with paliperidone. In 2 cases, TS symptoms were remarkably improved by switching from haloperidol to paliperidone extended release, and in another case, paliperidone-extended release showed significant efficacy in treating TS symptoms as the first-line drug. In all cases, no significant adverse side effects were detected.

Paradoxically, Fountoulakis and Panagiotidis [14] have report on the case of a female patient, age 22, suffering from schizophrenia, who developed a Tourette-like syndrome after treatment with paliperidone. Symptoms completely disappeared after she was switched to aripiprazole.

Paliperidone Palmitate Long-Acting Injectable in CAP Population

There is limited evidence for the use of long-acting formulations in CAP population. A recent observational study [15] with retrospective analysis of medical records showed 2.6% were prescribed second-generation long-acting injectable antipsychotics (SG-LAIAs); females (53%) slightly outnumbered males, mean age of 16.3 years, main diagnoses were psychosis (70%), and disruptive behavior disorders (30%); and primary reasons were poor compliance (90%) and/or poor insight. Second-generation SG-LAIAs used were aripiprazole (40%), risperidone (36%), and paliperidone palmitate (23%). The authors concluded that SG-LAIAs may be a safe treatment option during adolescence in inpatients with psychotic disorders, as well as with DBD. No differences were found in Clinical Global Assessment Scales improvement scores between the 3 SGA-LAIAs used, although patients on risperidone reported more side effects than those on aripiprazole.

Table 1. Uses of paliperidone in CAP population

Indication	Level of evidence*
Early-onset schizophrenia	Level I
Juvenile bipolar mood disorder	Level II–1
Autism spectrum disorder	Level II–1
ADHD	Level II–1
TS	Level II–3

* USPSTF rankings (1998).

Level I: evidence obtained from at least one properly designed randomized controlled trial.

Level II–1: evidence obtained from well-designed controlled trials without randomization.

Level II–2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from >1 center or research group.

Level II–3: evidence obtained from multiple time series designs with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.

Level III: opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

TS, Tourette syndrome; CAP, child/adolescent psychiatric; ADHD, attention-deficit/hyperactivity disorder; USPSTF, United States Preventive Services Task Force.

Of related interest, Mirza et al. [16] have reported on an adolescent male with schizophrenia. Following poor compliance with oral medications, a 4-week regimen of paliperidone palmitate long-acting injections was initiated, with an initial positive response. However, 10 days after the second dose, the patient developed severe acute-onset delirium with fluctuating levels of consciousness. Paliperidone palmitate was discontinued and the patient instead underwent a course of zuclopenthixol decanoate long-acting injections with a favorable outcome.

Conclusion

This overview has casted some light on paliperidone pharmacological portfolio and its therapeutic potential in CAP population. Paliperidone has some dynamic and kinetic superiority to the parent drug risperidone. Sound evidence base supports its use in early-onset schizophrenia, juvenile bipolar, and ASD. A modicum of evidence supports its use in TS and as adjuventia in ADHD. This is summarized in Table 1. We could not locate any reports of add-on use in major depressive disorder, obsessive-compulsive disorder, posttraumatic stress disorder, anorexia nervosa, or borderline behaviors as relevant to CAP population. Use of LAIAs, es-

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pecially for neuroprotection in CAP population, sounds attractive, at least from a theoretical perspective. However, this area is sorely underresearched and due to dearth of data, it is best not to use LAIAs in children and only cautiously off-label in adolescents who are older and within adult body weights. Definitely, larger rigorous studies would define the real place of paliperidone in child and adolescent psychopharmacotherapy. Until then, risperidone with its long track record in CAP population would remain a first option though.

Disclosures Statement

All authors declare no competing interests, nor financial affiliations, or industry-sponsored research.

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