

The prescribing pattern of paliperidone in a pediatric population

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ABSTRACT

OBJECTIVES: Paliperidone is a relatively new atypical antipsychotic, offers a potential new treatment option for adolescents, with several advantages including single dosage per day and availability in hepatic problems. However, there is a lack of efficacy and safety data for the use of this medication in various psychiatric disorders among children and adolescents. In this study, we retrospectively investigated the use of paliperidone in various psychiatric disorders among a youth population.

METHODS: The children and adolescents treated with paliperidone for any psychiatric problem at the outpatient and inpatient Child and Adolescent Psychiatry clinics of Düzce University Medical Faculty Hospital and Bakirkoy Mental Health Hospital were evaluated for the study. Data were collected retrospectively from the patient records. Patients' charts were reviewed to retrieve additional data on indications of the medications, adverse drug reactions (ADRs) and changes in the clinical condition. The clinical status of individual patients was assessed using the Clinical Global Index (CGI) score for severity and improvement.

RESULTS: The mean age of patients was 15.8 ± 1.3 years, and 59.6% ($n = 31$) of the group was male and 40.4% ($n = 21$) was female. Paliperidone was prescribed for median 150 days (quartiles 60 and 487 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 (BPDs) (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), autism spectrum disorders, 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 BPD or psychotic disorders. Of the 52 patients receiving paliperidone, 53.9% of patients were concurrently treated at some point with one or more than one of a psychostimulant/ADHD medication, an other antipsychotics, an antidepressant, a mood stabilizer, and any other class of psychotropic drug (such as a sleep medication). Totally, ADRs were recorded in 26 (50%) patients: weight gain ($n = 24$); extra pyramidal symptoms ($n = 8$); gastrointestinal system symptoms ($n = 4$); insomnia ($n = 2$); hyperprolactinemia ($n = 4$); sedation ($n = 2$); and skin affection ($n = 1$).

CONCLUSIONS: In this study group, paliperidone has been commonly used for schizophrenia, but it has also been used for mood disorders, DBDs, and Tourette's disorder in children and adolescents. Results showed clinically meaningful improvements in symptom measurements of different disorders. The drug is generally well tolerated and the most frequent adverse events include rigidity, akathisia, sedation, and increased appetite. Future prospective studies with large samples are needed for definite conclusions.

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Introduction

Paliperidone (9-OH-risperidone) is a metabolite of risperidone and differs from risperidone by only a single hydroxyl group which has permitted the synthesis of palmitate ester. Binding studies have shown a fast dissociation on D2 receptors and a relative greater effectiveness in the processes of intracellular signal transmission by paliperidone than its metabolic precursor. Like risperidone, paliperidone presents low risk for anticholinergic side effects,

including cognitive deficits and gastrointestinal disorders. Since both do not have antimuscarinic properties, paliperidone may offer some advantages over risperidone. Studies evaluating receptor affinity suggest that, paliperidone may have a lower incidence of orthostatic hypotension and may cause lower weight gain compared with risperidone. Moreover, paliperidone has several advantages including single dosage usage and can be preferable in patients with hepatic problems [1,2].

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Paliperidone was approved by the FDA in 2006 for the indication of the treatment of schizophrenia [3]. Recently, the FDA expanded the indication for paliperidone, to include relapse prevention of schizoaffective disorder using a long-acting injectable formulation of paliperidone; paliperidone palmitate [4]. Paliperidone appears to have comparable efficacy to haloperidol, perphenazine, risperidone, and olanzapine for the treatment of schizophrenia in adult patients. It was also declared to be an effective and generally safe for the treatment of schizophrenia or other psychotic disorders in adolescent patients and FDA-approved paliperidone in 2011 for the treatment of schizophrenia in adolescent patients [5]. Paliperidone was introduced in Turkey in 2013 and approved for the treatment of schizophrenia for 12- to 17-year-old adolescent patients. The drug is generally well tolerated in adolescents. It was recommended that defined daily dose (DDD) is 3–9 mg/day (once daily dosing) and maximum daily dose is 12 mg/day. The most frequent adverse events include tremor, hypertonia, dyspepsia, somnolence, akathisia, weight gain, and hyperprolactinemia [4].

Paliperidone also offers a potential new treatment option for a number of other psychiatric disorders in adolescents. There have been several retrospective review studies and case reports, suggesting safety and effective usage of paliperidone for the treatment of refractory bipolar manic or mixed episodes in adolescents and for treatment-resistant aggression, irritability, hyperactivity, self-mutilation in attention deficit hyperactivity disorder (ADHD), autism spectrum disorders (ASDs), and intellectual disability [5–9]. However, there is lack of data for the use of paliperidone in these various psychiatric disorders among children and adolescent patients [10].

Very little information has been existed on choices of clinicians about paliperidone prescription in youth population and studies investigating the paliperidone have generally been restricted with schizophrenia patients [11]. As far as Turkey is concerned, there has been no published data on paliperidone using in youth population. Thus, it is necessary to study the prescribing pattern, efficacy, and safety of paliperidone for pediatric patients. In this study, we aim to share our preliminary findings and clinical experience with paliperidone in a Turkish adolescent population.

Material and method

The present study represents a retrospective analysis of data from patients under 18 years of age; treated with paliperidone at an outpatient clinic of Duzce University Medical Faculty Hospital and inpatient clinic of Bakirkoy Mental Health Hospital in Turkey. Target population of the study was based on admission to aforesaid clinics between May 1, 2013 and December

31, 2015. The electronic medical records were reviewed using standardized data collection forms. Collected data included ages, gender, and psychiatric diagnoses according to Diagnostic and Statistical Manual of Mental Disorders criteria (DSM 5), treatment characteristics of paliperidone (duration and doses of paliperidone as well as all concurrently used antipsychotics, and other drugs). In addition to the electronic medical record, the clinicians' notes were reviewed to retrieve additional data on indications of the medications, ADRs and changes in clinical conditions. The study was conducted in accordance with the principles of Good Clinical Practices and the Declaration of Helsinki.

CGI-severity (CGI-S) and CGI-improvement (CGI-I) scores

Severity and improvement in symptoms were evaluated prior to administration of paliperidone and at the second month of treatment using the Clinical Global Impression-Severity (CGI-S: 1 = not ill, 7 = extremely ill) and the CGI-Improvement (CGI-I: 1 = very much improved, 7 = very much worse) scales (Conners and Barkley 1985). The CGI-S and CGI-I were assigned retrospectively in line with clinician's patient notes.

Statistical analysis

All analyses were conducted using Statistical Package for the Social Sciences 21 (SPSS) programme. Categorical variables were described in terms of proportions. Continuous variables were described in terms of mean, standard deviation, median, and range. Chi-square test was applied for categorical variables which are not normally distributed. Significance was set at a p -value $< .05$.

Results

Patients' characteristics

Records of 44,366 patients were reviewed and 71 patients treated with paliperidone were included in the study. Nineteen patients were excluded as they did not to come to follow-up visits and/or insufficient information in their case record for data collection. Fifty-two patients were finally selected for participation in the present study, 31 patients were male (59.6%), and 21 patients were female (40.4%). Mean age of the patient group was 15.8 years (SD ± 1.35).

Paliperidone prescriptions

Median use of paliperidone was 150 days (quartiles 60 and 487 days). Eighteen patients used paliperidone for

2–3 months (34.6%), 11 patients used paliperidone for 3–6 months (21.2%), 11 patients used paliperidone for 6–12 months (21.2%), and 10 patients used paliperidone more than 12 months (19.2%). Paliperidone was administered for therapeutic failure or ADR of an other antipsychotic treatment in 16 patients (31%). Mean dose of paliperidone was 7.6 mg/day (SD \pm 3.1). The daily dosage was between the range of 3–9 mg/day in 41 patients (78.8%). Only in 21.2% ($n = 11$) of the patient group, the daily dosage of paliperidone was above 9 mg/day. Average paliperidone dosage was significantly higher (9.8 mg/day) for using the treatment of psychotic disorders and bipolar disorders (BPDs) compared to disruptive behavioural disorders (DBDs) and anxiety disorders (4.7 mg/day; $p < .05$).

Paliperidone prescriptions according to psychiatric diagnosis

Paliperidone was prescribed for different diagnosis other than psychotic disorders considered as “off-label” in 35 patients (67.4%). The main indications for paliperidone prescription were; psychotic disorders ($n = 17$, 32.6%), BPDs ($n = 21$, 40.3%), and DBDs related with ADHD, ASD, conduct disorder (CD), oppositional defiant disorder (ODD), and mental retardation (MR) ($n = 12$, 23.0%) and also tic disorders comorbid with obsessive compulsive disorder (OCD) ($n = 2$, 7.9%) (Table 1).

Concomitant psychotropic medications

In total, 80.7% ($n = 42$) of the patients used the paliperidone as only antipsychotic, 19.2% of patients ($n = 10$) used paliperidone with one or more other atypical antipsychotics (AAP). The most used AAPs combination was aripiprazole ($n = 6$). Figure 1 showed prescription of concomitant psychotropic medications with paliperidone. Of the 52 patients receiving paliperidone, 10 patients were concurrently treated at some point with a psychostimulant/ADHD medication, 13 patients with an antidepressant, 14 patients with a mood stabilizer, and 9 with any other class of psychotropic drug.

Table 1. Mean paliperidone doses according to clinical diagnoses.

Mean paliperidone dose	PD	BPD	DBD	TD	
3 mg	<i>N</i>	0	5	5	2
	%	0.0	33.3	0.0	50.0
6 mg	<i>N</i>	10	6	7	2
	%	58.3	16.7	50.0	50.0
9 mg	<i>N</i>	2	5	2	0
	%	8.3	25.0	0.0	0.0
12 mg	<i>N</i>	5	5	1	0
	%	33.3	25.0	50.0	0.0
Total	<i>N</i>	17	16	15	4
	%	100.0	100.0	100.0	100.0

Note: BPD: bipolar disorder; DBD: disruptive behavioural disorder; PD: psychotic disorder; TD: tic disorders.

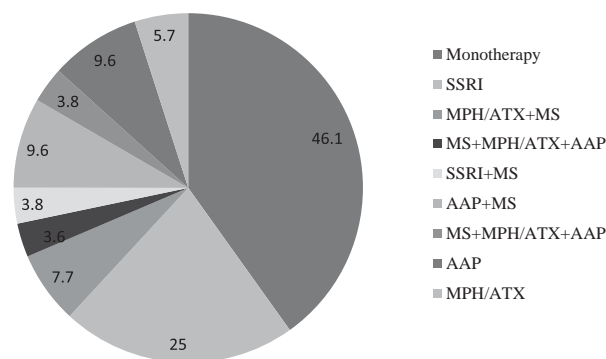


Figure 1. Concomitant psychotropic medications using percentages with paliperidone. AAP: atypical antipsychotic; ATX: atomoxetine; MPH: methylphenidate; MS: mood stabilizer; SSRI: selective serotonin reuptake inhibitor.

Adverse drug reactions

Totally, ADRs were recorded in 26 (50%) patients: weight gain ($n = 24$); extra pyramidal symptoms (akathisia, tremor, parkinsonism, muscular rigidity, acute oro-facial dystonia) ($n = 8$); gastrointestinal system symptoms (dyspepsia, nausea, and vomiting) ($n = 4$); insomnia ($n = 2$); hyperprolactinemia ($n = 4$); sedation ($n = 2$); and skin affection ($n = 1$). The recorded reasons for discontinuation paliperidone were; intolerable ADR ($n = 9$), deterioration ($n = 2$), lack of effect ($n = 8$), and other reasons ($n = 1$).

CGI-S and CGI-I scores

The changes in CGI-S and CGI-I scores at the first and third hospital visits were shown at the Table 2. One patient missed the third visit (about 2 month after the first visit). Notes of changes in the clinical condition were available in 51 cases (98%), 45 (88.2%) of who had signs of clinical response, whereas 6 patients (11.5%) did not respond.

The mean CGI-S scores were similar for all diagnoses (psychotic disorders = 4.5, bipolar disorders = 4.6, tic disorders = 4.3, and DBDs related with

Table 2. Distribution of CGI-S and CGI-I scores.

CGI	<i>N</i>	%
CGI-S		
Moderately ill	7	13.5
Markedly ill	26	50.0
Severely ill	18	34.6
Extremely ill	1	1.9
Total	52	100.0
CGI-I		
Very much improved	3	5.8
Much improved	27	51.9
Minimally improved	15	28.8
No change	5	9.6
Much worse	1	1.9
Total	51	98.1
Missing	1	1.9
Total	52	100.0

Note: CGI: Clinical Global Index; CGI-S: Clinical Global Index Severity; CGI-I: Clinical Global Index Improvement.

ADHD, ASD, CD, ODD, and MR = 4.5, $F_{(2,235)} = 0.11$, $p = .89$) at the beginning of the treatment. The mean CGI-I scores were also similar for all diagnoses (psychotic disorders = 2.5, BPDs = 2.8, tic disorders = 1.9, and DBDs = 1.9, $F_{(1,23)} = 0.21$, $p = .19$) at the third months of the treatment. Analysis of variance did not show statistically significant differences for mean CGI-I scores ($F_{(2,235)} = 1.8$, $p = .18$). However, following stratification of CGI-I into aggregated groups, (A) = (1) and (2), (B) = (3) and (4), and (C) = (5), (6), and (7), BPDs were associated with the lowest proportion of patients being assigned CGI-I category (A) (1, very much improved or 2, much improved); ($\chi^2 = 11.0$, d.f. = 4, $p = .026$).

Discussion

In the present study, the use of paliperidone was shown to improve CGI-I scores and reduced the severity of psychotic disorders and contributed to improvements in clinical symptoms in children and adolescents. Results also showed clinically meaningful improvements in symptoms of BPDs, Tourette's disorder comorbid with OCD and DBDs related with ADHD, ASD, CD, ODD, and MR. Most patients in the present study did not experience side effects, and absolutely no serious or fatal side effect was observed; the use of paliperidone is considered to be safe. Also disturbing side effects such as rigidity, sedation, and akathisia were observed in less than 25% of subjects.

Doses and duration of paliperidone

DDD of paliperidone is between 3 and 12 mg/day [4]. The average dose prescribed when antipsychotic medications were used off-label varied considerably across drugs and diagnostic groups. In the present study, the doses of paliperidone ranged between 3 and 12 mg/day. Doses tended to be higher for patients with psychosis or BPDs, and lower for patients with adjustment reaction or anxiety disorder. This suggests that clinicians are tailoring their choice of drug and prescribed dose to the particular characteristics of the patient.

Off-label use

We found a considerable degree of off-label use of paliperidone, with 67.4% of patients who were given paliperidone having no visit with a diagnosis of either schizophrenia. The use of AAPs for indications not approved by the FDA accounts for the majority of treatment with AAPs [12–14]. Because there has not been enough data about safety and efficacy of these drugs for non-FDA-approved indications; a large proportion of youth patients treated with antipsychotic for “off-label” indications [10]. A recent analysis by the

Agency for Healthcare Research and Quality reported that diagnoses of ADHD, anxiety, dementia in elderly patients, depression, eating disorders, insomnia, OCD, personality disorder, post-traumatic stress disorder, substance abuse disorders, and Tourette's syndrome were treated with atypical antipsychotics despite varying evidence of efficacy in the literature [15]. A separate analysis of 11,700 Arkansas Medicaid-covered children who were newly treated with AAPs also found the most common condition was ADHD followed by depression, CD, ODD, and adjustment reactions [16]. Rettew et al. evaluated the AAP prescribing in children enrolled in USA Medicaid and found that aggression (62.9%) and mood instability (55.6%) were the two primary target symptoms for which antipsychotic medications were being used and the most common diagnoses were mood disorders and ADHD [17]. There are several reasons why paliperidone is used off-label in the present sample. The efficacy data may not exist for some conditions or populations (e.g. children), although manufacturers have a powerful incentive to conduct clinical trials to show efficacy in conditions other than those for which their drug has been approved for use. Another possible explanation for high rate of off-label use in the present study is that clinicians tried these medications as a last resort in patients who have not responded to other treatments. A high rate of off-label paliperidone use would not necessarily be of concern if there were scientific evidence supporting the effectiveness of this medication for conditions other than schizophrenia. Since 2003, antipsychotic medications have been approved by the FDA for the treatment of other disorders in addition to schizophrenia and BPD: risperidone and aripiprazole for irritability in autism, aripiprazole, olanzapine, and quetiapine for adjunctive use with antidepressants in patients with treatment-resistant depression [18]. Hence, such uses of these drugs would not be considered off-label today, although they were at the time these data were collected. However, evidence supporting the effectiveness of paliperidone for other disorders is generally lacking or weak [10].

The main off-label use for the paliperidone was DBDs related with ADHD, ASD, CD, ODD, and MR in the present study. The rate of visits for mental health issues for children and adolescents is increasing at a much faster rate than for adults, and disruptive behaviour is now the most common mental disorder diagnosis in youth [19]. Antipsychotics have been shown to reduce aggression, and practice guidelines support the appropriate use of atypical antipsychotics in youth [20–22]. Risperidone has shown evidence for efficacy in disruptive behaviours [23]. Aripiprazole and risperidone are also FDA-approved medications for behavioural disturbances (irritability and aggression) associated with autism and/or intellectual

disabilities in children and adolescents (age 6–17 years) [24,18,25].

An exploratory study in a Canadian ADHD clinic found that nearly one in five children with ADHD was prescribed AAPs off-label to treat ADHD in 2009 [26]. Pathak et al. [16] assessed the dispensing pattern of AAPs using Arkansas Medicaid claims data and reported ADHD as the most common condition for children and adolescents to be prescribed AAPs. The clinical use of AAPs in paediatric patients with ADHD alone is not fully justified due to the limited evidence from randomized control trials. Existing clinical trials of AAPs for ADHD had mixed findings in terms of efficacy and were conducted in children with severe comorbid conditions, such as disruptive behaviours, BPD or MR [27,23,28]. In most of these studies, the AAP was targeted at the comorbid symptoms rather than ADHD itself. In 2004, a consensus of international experts on ADHD and DBDs suggested augmenting psychostimulant treatment with risperidone as a second-line treatment option for the DBD in children with ADHD and conduct disorders [29]. An open-label trial evaluated the treatment of behaviour disorders with paliperidone in children with previously treated with risperidone and found similar efficacy with risperidone [6]. Also paliperidone treatment was associated with significant improvement in irritability in adolescents and young adults with autistic disorder [8–9]. However, the debate about the role for AAPs in non-psychotic mental disorders still remains because there is no specific indication, but also because of the documented increased risk of various side effects of AAPs [14].

In addition to schizophrenia, most second-generation antipsychotics have also been approved to treat BPD [30,31]. As of March 2010, aripiprazole, olanzapine, quetiapine, and risperidone are FDA approved medications for bipolar mania in children and adolescents (age 10–17 years; except olanzapine, age 13–17 years) and for adolescent schizophrenia (age 13–17 years) [24]. In line with the published data in adults, the results of this study show that paliperidone is widely used in those with BPDs [32,33]. According to literature, mood stabilizers and atypical antipsychotics are currently the most frequently considered primary drugs for the treatment of paediatric BPD [31,10]. Retrospective studies on the efficacy and safety of atypical antipsychotic agents for patients with paediatric BPD have been conducted [34] Paliperidone extended-release is not currently FDA labelled for BPDs; however, to date, there have been three published randomized controlled studies evaluating the efficacy and safety of treating adult patients with BPDs. Double-blind placebo-controlled studies on long-term maintenance treatment with AAP in children and adolescents are also currently in process [35,36]. Two of these evaluated paliperidone as monotherapy and the

other assessed adjunctive therapy. According to these evidence, paliperidone at higher doses of 9–12 mg/day may be a safe and efficacious treatment option for acute episodes of mania in BPD [37]. Also in a prospective open-label trial, efficacy of paliperidone monotherapy for the treatment of bipolar spectrum disorders in children and adolescents was shown [38]. Risperidone is FDA approved for the treatment of BPDs in adults based on clinical data demonstrating efficacy. So Paliperidone is the major active metabolite of risperidone and has many similarities with its major compound that may contribute to potential efficacy in the treatment of manic episodes in BPDs. In the present study, 14 patients received mood stabilizers in addition to paliperidone. In addition, 10 of the patients were given paliperidone plus methylphenidate and atomoxetine. Even though we cannot determine whether their improvement was due to the paliperidone or to other medications, the paliperidone may have had some influence on the BPDs symptoms [14].

The most common ADRs of AAPs are metabolic (weight gain, obesity, dyslipidemia, hyperglycaemia, diabetes, insulin resistance), cardiac, neuromotor (somnolence/sedation, extrapyramidal syndrome, akathisia, dystonia, catatonia), and endocrine (hyperprolactinaemia) [24]. More than 40% of patients who were administered paliperidone in the present study did not experience side effects, and absolutely no serious or fatal side effect was observed. We observed acute oro-facial dystonia during the follow-up, leading to the discontinuation of paliperidone treatment in three patients. As no serious side effects were observed, the use of paliperidone for patients is considered to be safe.

Limitations

A number of limitations are associated with these administrative data. First, it used a retrospective design that relied on chart reviews. Thus, no placebo-control group was included, and the review process may have been biased because assessments of diagnoses, treatment effects, and side effects were made retrospectively based on charts. Second, the intervals between hospital visits were not exactly consistent among patients, and this may have adversely affected our assessment of treatment effects. Thirdly, although detailed information is available on the medication and dose prescribed and days of supply, we cannot determine what condition paliperidone is intended to treat since many patients received multiple psychiatric diagnoses. Hence, while we can determine whether a patient who was prescribed paliperidone had a diagnosis of major depression, we cannot say that the diagnosis of depression was the reason for the paliperidone prescription. In addition, diagnoses are based on ICD-9-CM codes, which may be miscoded or incomplete.

This could be particularly problematic for serious mental disorders like schizophrenia, which may be underreported due to stigma associated with the diagnosis. Also, it could be argued that the results were biased because our results represented only tertiary hospitals and the number of subjects is too small to permit generalizations based on study results.

Despite these limitations, the present study used a naturalistic chart-review design that reflected actual prescribing patterns and yielded data on treatment effects and side effects from a clinical setting. Thus, it provides practical information that can be used for clinical purposes. However, these results must be confirmed in the future through multi-center, double-blind, placebo-controlled studies.

Conclusion

Our results reflect the particular use of paliperidone in the present study population. In line with the published data, the results of this study show that paliperidone are generally used in those with psychotic disorders. These findings also underline the widespread off-label use of paliperidone in the treatment of other psychiatric disorders. However, the role for these medications in non-psychotics mental disorders still remains unclear since there is no specific indication, but also because of the documented increased risk of various side effects of paliperidone. This study also highlights the important differences existing among guidelines' recommendations and physicians' paliperidone prescribing behaviour for psychiatric patients.

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The study was carried out with the approval of the responsible ethics committee and in accordance with national law and the Helsinki Declaration from 1975 (in its current revised form).

Disclosure statement

No potential conflict of interest was reported by the authors.

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