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To cite this article: Oznur Yilmaz Bayer , Ipek Turktas , Hacer Ilbilge Ertoy Karagol , Sebnem Soysal & Dilek Yapar (2020): Neuropsychiatric adverse drug reactions induced by montelukast in children with asthma impair their quality of life, Journal of Asthma, DOI: [10.1080/02770903.2020.1861626](https://doi.org/10.1080/02770903.2020.1861626)

To link to this article: <https://doi.org/10.1080/02770903.2020.1861626>



Accepted author version posted online: 07 Dec 2020.



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Neuropsychiatric adverse drug reactions induced by montelukast in children with asthma impair their quality of life

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ABSTRACT

Introduction: Montelukast-induced neuropsychiatric adverse drug reactions (ADRs) have been reported in retrospective studies. This study aimed to reveal the neuropsychiatric ADRs triggered in patients taking montelukast due to asthma in real time, and to evaluate the effect of these ADRs on quality of life (QoL).

Methods: Patients, ages 3-18 years, taking montelukast for the first time and their parents were included. Ages 3-7 years were defined as the preschool and ages 8 – 18 years as the school-age group. At the beginning of the study and at the end of the second week of treatment, the neuropsychiatric complaint assessment questionnaire and the KINDL QoL scale were administered to patients and their parents. The effect of ADRs on the decrease in QoL was evaluated by multivariable logistic regression.

Results: Neuropsychiatric ADRs were reported in 78 (62.4%) of 125 patients, who recovered when the drug was discontinued. Temperamental behavior, nightmares and sleep disorders occurred significantly more often in both groups compared with pre-treatment ($p < 0.001$ for each). In both groups, except in the child-reported family relationships subscale in the school-age group, significant decreases were found in both child and parent proxy-reported QoL total/sub-scores compared with pre-treatment ($p < 0.001$ for each).

It was found in the evaluation that the overall QoL of those experiencing ADRs in both age groups was more affected. (Child-reported QoL $OR_{\text{pre-school age}} = 2.66$, $p = 0.048$; $OR_{\text{school-age}} = 5.95$, $p = 0.027$; parent-proxy QoL $OR_{\text{pre-school age}} = 3.52$, $p = 0.010$, $OR_{\text{school-age}} = 6.43$, $p = 0.027$)

Conclusions: Montelukast-induced neuropsychiatric ADRs are more frequent than reported in the literature and negatively impact children's QoL.

Keywords: Quality of Life, Treatment, Pediatrics, Pharmacotherapy

Introduction

In childhood asthma, the first choice in providing symptom control for all age groups is inhaled corticosteroids (ICS) (1, 2). However, some systemic adverse effects that may occur during the administration of ICS cause concern in both parents and physicians (3, 4). Guidelines recommend montelukast as an alternative drug to ICS in persistent asthma (1, 2, 5). The fact that these drugs have oral forms such as granules and chewable tablets provides ease of use in children when compared with inhaler anti-asthmatic drugs. This is therefore the reason this drug is chosen in treatment (1, 6-8). In addition, montelukast is also recommended in guidelines for the treatment of diseases comorbid with asthma such as allergic rhinitis and chronic urticaria (9, 10). However, it has increasingly been reported that montelukast causes neuropsychiatric adverse drug reactions (ADRs), leading to sleep disorders, changes in behavior and mood, and other conditions (11-16).

A great number of studies have explored the factors that influence quality of life (QoL) in children with asthma (17, 18). These studies evaluate the effect of disease-specific parameters such as the severity of asthma and control levels on QoL but so far, the effect of ADRs on QoL related to the drugs used in treatment has not been investigated (17, 18).

Neuropsychiatric ADRs related to the use of montelukast in asthmatic patients have so far been evaluated through retrospective studies. Our first aim in this study is to determine in real time the neuropsychiatric ADRs that occur due to montelukast in patients who are initiated with montelukast due to asthma. Our second aim is to evaluate the effect of these neuropsychiatric ADRs on patients' QoL.

Methods

Study populations

This prospective, observational study was conducted in the outpatient clinic of the Pediatric Allergy and Asthma Department of Gazi University Hospital between September 2013- March 2014. Patients between the ages of 3-18 years who were started on montelukast for the first time due to asthma and their parents were included in the study. Patients between the ages of 3-7 years were defined as the preschool-age group and patients between ages 8 – 18 years as the school-age group. Patients experiencing an asthma attack when started on montelukast and patients with uncontrolled asthma symptoms were excluded from the study. Patients who had an additional physician-diagnosed chronic disease outside of asthma (e.g., diabetes mellitus, chronic renal disease) and those who had a physician-diagnosed neuropsychiatric disease (e.g., epilepsy, attention deficit hyperactivity disorder) were also excluded. All of the data were obtained through face-to-face interviews by interviewing the patient and their parents separately. Baseline demographic and clinical characteristics, including age, gender, and the atopic status of the patients, were gathered from the patients' file. Written informed consent was obtained from all parents and children ≥ 12 years old. This study was approved by Gazi University Ethics Committee.

Study design

Every patient treated for an asthma diagnosis (e.g., ICS, montelukast, salbutamol) in our clinic and/or their relatives are given medication training on the use of the drug and possible side effects. An inhalation technician provides this instruction in written form.

Each patient evaluated by the allergy physician and prescribed montelukast for asthma was referred to Yılmaz Bayer O (YBO) after receiving drug training. Patients whose pharmacy records indicated

that they had not used montelukast previously were invited to participate in the study. Afterwards, psychologist Soysal S (SS) administered a neuropsychiatric complaints assessment questionnaire and a QoL scale to whichever parent of the patient had agreed to participate in the study. The psychologist SS evaluated the neuropsychiatric state of the patient and applied the QoL scale to the patient as well. A diary was provided to the parent for recording the use of montelukast and any complaints that had emerged. The patients and their parents were asked to call SS and come to the clinic whenever there was any condition that they associated with the drug in the following 2 weeks when this occurred 3 days in a row. If this was not the case, they were told to come in for a checkup at the end of the second week.

When the parent called SS about any complaints related to the drug, the drug was discontinued if the investigators assessed (YBO, Ertoý Karagol HI, Turktas I) it to be related to montelukast after receiving detailed information. The patient and parents were then called into the clinic. The neuropsychiatric complaints questionnaire (parent) and a QoL (patient and parent) scale were re-administered by SS to these patients on the day they came back to the clinic. In the neuropsychiatric complaints evaluation, a detailed investigation was made as to how the complaint had improved after the discontinuation of montelukast and how many days it took to improve. The diaries and empty montelukast boxes brought in by the parents were also evaluated. At the end of the second week (the end of the study), the same questionnaires were re-applied to the patients who did not develop ADRs in the follow-up and to their parents.

Monitoring of asthma and accompanying comorbidities

The allergist in the asthma clinic monitored the patient's asthma and accompanying comorbidities in the study period. Symptom control, physical examinations of the patients at the beginning of the treatment and afterwards, exacerbations of asthma in the follow-up period, urgent applications for medical aid, hospitalizations, comorbidity status and the need for extra treatment were evaluated and all recorded in the patient files.

Neuropsychiatric complaints assessment questionnaire

The researchers drew up the neuropsychiatric complaints assessment questionnaire based on the neuropsychiatric events outlined in the summary of product characteristics for montelukast (19). The questionnaire contained items on changes in behavior and mood, nightmares, difficulty falling asleep, irritability, feelings of anxiety and restlessness (answered as yes-no), the frequency and duration of these symptoms, if any (answered as rarely, frequently, or always), and with what the individuals associated these experiences.

QoL assessment questionnaire

Two different questionnaires were implemented: the Kinder Lebensqualität Fragebogen (KINDL) Pediatric QoL Questionnaire was based on an interview with the patient and the KINDL Family QoL Questionnaire contained the responses of the patient's parent (20). KINDL is a generic scale developed by Ravens-Sieberer et al. that was tested for reliability and validity by Eser et al. in Turkey (21, 22). This scale makes use of three forms based on self-reporting that have been drawn up for use in different age groups. These are the Kiddy-KINDL form for children between the ages of 4-7, the Kid-KINDL form for children between the ages of 8-12, and the Kiddo-KINDL form for adolescents, ages 13-16. Parent forms are applied to the parents of 4-7-year-old children and parents of children, ages 8-16. These questionnaires are based on a Likert-type scale. All KINDL scales consist of 6 subscales about physical well-being, emotional well-being, self-esteem, family and friends, school (preschool/kindergarten where daily activities are carried out), and 6 additional

questions that receive responses if there is a chronic disease. On the other hand, the parental scale applying to children, ages 4-7, includes the additional domain heading of “Other important issues.” Mean total/subscale scores are expressed in values of between 0-100. High scores are indicators of high QoL. The Kiddy-KINDL child and parent forms were administered to cooperating 3-4-year-old patients and their parents.

Statistical analysis

Statistical analysis was performed using the SPSS 20.0 (Chicago IL) computer program. Categorical variables were given as numbers and percentages, and continuous variables were presented with medians and interquartile range (IQR) for descriptive analysis. Normal distributions for continuous variables were assessed with visual (histograms and probability graphics) and analytic methods (Kolmogorov-Smirnov and Shapiro-Wilk’s test). Chi-square tests were used for the comparison of categorical variables between groups. The pre-treatment and post-treatment neuropsychiatric appearance of ADRs was compared using the McNemar test. QoL scores are presented as medians (IQR). The Mann Whitney U test was used for the comparative analysis of scale scores between two independent groups. The Wilcoxon signed rank test was used to analyze statistically significant differences in the QoL scores before and during the ADRs. The relationships between QoL scale scores were assessed using Spearman’s correlation analysis.

The development of neuropsychiatric ADRs and the effect of age and gender on the decrease in QoL scores after treatment were evaluated by multivariable logistic regression. Our dependent variable, the amount of change in the QoL score, was turned into a dichotomous variable, taking into account the distribution of QoL scores. Patients who experienced a decrease in scores of 10% or more after treatment compared to pre-treatment were accepted as patients with a decrease in QoL. They were accordingly, dichotomized as patients with a decrease of $\geq 10\%$ in QoL scores, and patients with a decrease of less than 10% or those whose QoL score did not change. Statistical significance was accepted as $p \leq 0.05$.

Results

Demographics

Of the 127 patients consenting to participate in the research, 2 did not complete the study. These 2 patients could not come for a control visit 2 weeks later because they lived outside the city. The median age of the remaining patients was 4.5 (4-8) years; 58 of the patients (46.4%) were female. Ninety-two patients (73.6%) were younger than 8 years old and in the preschool-age group. No difference was found between preschool and school-age patients in terms of gender ($p=0.088$). The comparison of demographic characteristics of both groups is given in table 1.

During the course of the study, none of the patients had an asthma attack, none applied to the emergency room due to an attack, and no hospitalizations occurred. No comorbid condition accompanying asthma and requiring treatment was noted.

Assessment of the development of Neuropsychiatric ADR

While temperamental behavior, nightmares and sleep disorder were reported to be rare and only seen in 1 patient in the preschool-age group before the montelukast treatment was started, the questioned neuropsychological complaints were not reported in any of the patients in the school-age group at the start of the treatment. During the study period, neuropsychiatric ADRs appearing while taking montelukast were reported in 78 (62.4%) of the patients. Our figure provides the distribution of

ADRs separately for both age groups. The most frequently reported ADR in both groups was temperamental behavior. This was followed by nightmares, sleep disorders (insomnia, having difficulty falling asleep), hallucinations and headaches. Temperamental behavior, nightmares and sleep disorders were significantly higher in both groups when compared with pre-treatment ($p < 0.001$ for each). While hallucinations exhibited statistical significance in only the preschool-age group when compared with pre-treatment ($p < 0.001$), headache was not found to be significant in either group when compared to pre-treatment. When both groups were compared in terms of the appearance of ADRs, no difference was found between the age groups ($p = 1.00$). The appearance of ADRs was not different in terms of gender in the groups (preschool age $p = 0.60$; school-age $p = 0.13$).

Apart from these reported adverse effects, depressive symptoms were seen in one patient in the preschool-age group on the seventh day of treatment; night terror (crying during sleep, restless sleep) was seen in one patient in the school-age group. In both patients and in all other patients who were found to exhibit ADRs, these neuropsychiatric complaints disappeared in three days with the discontinuation of the montelukast treatment.

Assessment of QoL

Table 2 shows pre-treatment and post-treatment QoL total and sub-scores as reported by both age groups and the parents. There was a difference between the total QoL scores reported by the patient and their parents at the beginning and end of the treatment in the preschool-age group ($p < 0.001$ for both). In the school-age group, the total QoL scores reported by children and parents were found to be similar at pre-treatment and post-treatment ($p = 0.138$, $p = 0.073$ respectively).

When both age groups were evaluated in terms of the relationship between child-reported total QoL and parent proxy-reported total QoL, a moderate to strong relationship was found between pre-treatment and post-treatment ($r = 0.60-0.89$).

In both groups, except in the child's reported family relationships subscale in the school-age group, statistically significant decreases were found in both child-reported and parent proxy-reported QoL total and sub-scores when compared with pre-treatment (Table 2).

The effect on QoL of Montelukast-induced neuropsychiatric ADRs

The effect of experiencing neuropsychiatric ADRs on the decrease in QoL was examined by multivariable logistic regression analysis (Tables 3 and 4). In the preschool-age group, it was found that the total QoL (model IX; OR = 2.66) and family relationships (model IV; OR = 4.05) of those who experienced ADRs were more affected according to the children's own statements. According to parents' statements in this group, the total QoL (model IX; OR = 3.52), self-esteem (model III; OR = 3.15), family relationships (model IV; OR = 3.56) and other important issues (model VII; OR = 12.56) were found to be more affected (Table 3).

In the school-age group, it was found according to the children's statements that the total QoL (model VIII; OR = 5.95), emotional well-being (model II; OR = 7.33) and family relationships (model IV; OR = 16.86) were more affected. According to parental statements, it was found in this group that the total QoL (model VIII; OR = 6.43), self-esteem (model III; OR = 9.83) and friends relationships (model V; OR = 6.40) of those who had ADRs were more affected (Table 4).

Discussion

An evaluation of neuropsychiatric ADRs in asthmatic children who were initiated on montelukast in real life and their effects on QoL was carried out for the first time in this study. The results of this study draw two very clear conclusions. The first conclusion is the fact that montelukast-induced neuropsychiatric ADRs are much more frequent than reported in the literature, and the second is the fact that these neuropsychiatric ADRs had negative impacts on children's QoL.

Based on the literature, we believe that our detection of a very high rate of ADRs (62.4% vs. 16%) can be explained by both the prospective order and the design of our study (13). In accordance with the study design, we informed the parents of the patients about the neuropsychiatric ADRs that may develop due to montelukast and we looked for the presence of neuropsychiatric complaints at the beginning of the study. This was useful in increasing the awareness of parents about this issue. After starting treatment, we closely monitored each patient for the development of neuropsychiatric ADRs by being in communication with their parents. Naturally, this prior information and close communication may have increased the tendency of parents to associate neuropsychiatric complaints with montelukast. On the other hand, sleep disturbance, irritability, or having nightmares may have some familial or social reasons that we cannot control and are not reported to us. However, we know at least that these neuropsychiatric complaints did not develop because of asthma or another organic comorbidity during the study.

Moreover, over the course of our study, we detected montelukast-triggered situations such as irritability, nightmares or sleep disturbance as soon as these complaints started. If we had seen these patients in the first or third month of montelukast treatment, however, they would have perhaps gotten used to these ADRs and accepted them as normal. Furthermore, as the drug continued to be taken over time, tolerance to these ADRs would develop and they would not be reported. We therefore think it is important, in terms of detecting montelukast-induced ADRs, to catch them at their onset.

In other studies that evaluate neuropsychiatric ADRs associated with montelukast, data have been evaluated retrospectively through pharmacovigilance records and/or patient files (14, 15). In the study of Benard et al., patients using montelukast were detected through the hospital database (13). Patients' parents who remembered the montelukast treatment were questioned about the period when montelukast was used and the frequency of ADRs was evaluated (13). The ADRs reported in these studies depend on the associations that the patient and/or parent and the attending physician made between the drug and the resulting situation or on their awareness of the situation at the time. These adverse reactions may have occurred but not been reported because they had not been associated with the drug (14, 15). For this reason, unlike in our study, evaluations of whether the reported ADRs were related with montelukast were made at a later date using a statistical method, through scoring and/or based on the reports of a committee of experts (13-15). In our study, however, the patients were followed up with standard tests and by the same team of physicians after the drug was started, and it was found that the ADRs disappeared completely after the drug was discontinued. We believe that this close monitoring allowed us to become aware of these montelukast-related ADR's in a shorter period of time.

Also, another reason for our high rate of detecting ADRs, or a condition contributing to this, may be ethnic differences. It is known that the prevalence of asthma and morbidity-mortality rates associated with asthma differ between ethnic groups (23). The question however is whether there are ethnic differences in terms of drug responsiveness and ADRs related to asthma drugs. Very little is known on this issue (24). There is therefore a need for pharmacogenomic studies that compare different ethnic groups in terms of ADRs that develop due to montelukast and other asthma drugs (23, 24).

Similar to other studies in the literature, we also found that the most common neuropsychiatric ADRs that developed with the administration of montelukast at all ages were behavioral and sleep disorders

such as temperamental behavior and nightmares (13, 15). Unlike our study, Perona et al. reported that neuropsychiatric types of ADRs differed according to age groups (15). In this study, it was reported that much more serious conditions such as depression or psychotic disorder were more frequent in adolescents but it was found that these took longer to develop. Relatively milder conditions such as sleep and behavior disorders were more frequent in younger age groups and these developed much earlier than depression or suicidal behavior (15). There is one instance in the literature, however, where a 12-year-old adolescent case was reported to have developed serious depression in a short period of time while on montelukast therapy (25). In addition, our study revealed the appearance of depressive symptoms in one of our patients, a 4-year-old, in the first week of treatment; this patient's symptoms receded with the discontinuation of the drug. Thus, we think we cannot say that the type of adverse drug reaction and its severity changes depending on the period of time the drug is used. It is emphasized that the negative impact of montelukast on the central nervous system (CNS) occurs as a result of blood passing the barrier of the brain to affect the leukotriene receptors in the CNS (25). Although this premise has partly been supported by animal studies, it has not been shown precisely which mechanisms cause the negative impact of montelukast on the CNS (26-28).

The adjudication committee formed in the study of Benard et al. evaluated the severity of ADRs and concluded that reaction severity differs between mild to very mild (13). However, we did not evaluate the severity of the ADRs that emerged in our study. None of our patients developed a reaction that could be defined as a serious adverse drug reaction (29). On the other hand, we believe that the ADRs that did develop cannot be defined as mild because we found that these montelukast-induced reactions caused a decline in QoL in the post-treatment when compared with pre-treatment in both groups. In children who are at an age when it is difficult to express oneself, evaluating QoL with scales that only apply to children may not be sufficient (30). For this reason, QoL was evaluated not only on the basis of the child's declarations but also through the parents' statements. A decrease was found in the QoL total/subscale scores declared by the parents of both preschool and school-age children when compared with pre-treatment, and it was thought that the development of ADRs had an influence on this decrease. When the decrease in the QoL subscale scores was evaluated, it was found that the parents of the preschool-age group stated that the children's relationships with family, their children's self-esteem and other important issues deteriorated due to the ADRs that had developed. The parents of the school-age group also stated that their children's self-esteem and relationships with friends had deteriorated because of the ADRs. In terms of the children, while the preschool-age children perceived deterioration in their family relationships, school-age children perceived deterioration in their family relationships and in their emotional well-being. It is very clear that sleep disorders such as insomnia and nightmares within a week of starting montelukast and perhaps the aggression that occurs due to these disorders will cause deterioration in children's communications with family and in their social life, adaptation to school and their school achievement.

There were limitations to our study. The first of these is the absence of a control or placebo group. Because the parents were explicitly informed about the behavioral changes, nightmares, and other reactions, they may have become more attentive in this respect. A placebo group could have given more insight into the causality of such side effects. Another limitation of our study was the fact that a drug re-challenge was not conducted. However, since the parents observed that neuropsychiatric conditions improved with the discontinuation of montelukast, we thought that it would not be ethical to recommend that the children take montelukast again.

In conclusion, it can be said that a large number of asthmatic children can exhibit or declare when asked, that they experience behavioral issues and sleep disorders that adversely affect their QoL. For this reason, it would be useful in terms of evaluating the patient's neuropsychiatric condition to take a detailed medical history before initiating montelukast treatment. Informing parents about the ADRs

induced by montelukast and closely monitoring patients after the initiation of treatment would be appropriate.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Funding

This study did not receive any external funding.

Acknowledgements

The authors report no acknowledgements.

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Table 1. The comparison of demographic characteristics for both age groups

	Preschool age (n=92)	School age (n=33)	p
Median age, years (IQR)	4 (3-5)	8 (8-9.5)	<0.001
Gender, Male	54 (58.7)	13 (39.4)	0.088
Physician's assessment of asthma control			0.649
Well controlled	7 (8.0)	1 (3.0)	
Partly controlled	85 (92.0)	32 (97.0)	
Medication at index visit			
Initiated on montelukast only	55 (59.8)	6 (18.2)	<0.001
Montelukast added to ICS	37(40.2)	25 (75.7)	0.021
Montelukast added to ICS+LABA	0	2 (6.1)	-
Patients with ≥ 1 acute care visit	74 (80.4)	12 (37.5)	0.011
Patients with ≥ 1 hospital admission	20 (22.7)	2 (8.3)	0.814
Presence of atopic sensitization	13 (14.1)	14 (41.7)	0.002
Personal history of atopic diseases	20 (22.7)	14 (41.7)	0.039
Family history of atopic diseases*	49 (53.2)	23 (70.8)	0.151

Data are presented as n, median (interquartile range (IQR)) or n (%). ICS: inhaled corticosteroid; LABA: long-acting β_2 -agonist.

*: in a first-degree relative (parent or sibling)

Table 2. Comparison of pre-treatment and post-treatment QoL scores in both age groups and the parents

Scale	Child self-reported			Parent proxy-reported		
Preschool-age (n=92)	Before treatment	After treatment	p*	Before treatment	After treatment	p*
Physical well-being	83.33(83.33-100)	66.66(66.66-83.33)	<0.001	85 (80-90)	70 (65-80)	<0.001
Emotional well-being	100(83.33-100)	83.33(83.33-83.33)	<0.001	95 (90-95)	85 (75-90)	<0.001
Self-esteem	100 (100-100)	100 (83.33-100)	<0.001	100 (81.25-100)	80 (75-90)	<0.001
Family	100 (100-100)	100(66.66-100)	<0.001	90 (80-90)	80 (70-85)	<0.001
Friends	100 (100-100)	100(83.33-100)	<0.001	100 (85-100)	85 (75-93.75)	<0.001
Nursery-kindergarten	100 (100-100)	83.33 (66.66-100)	<0.001	95 (85-100)	80 (70-85)	<0.001
Other important issues	-	-	-	85.90 (81.81-89.09)	78.18 (73.63-81.81)	<0.001
Total	83.33(77.77-97.22)	77.77(69.44-86.11)	<0.001	82.82(78.26-90.43)	74.34(69.23-79.45)	<0.001
Disease perception	72.20(61.11-81.94)	61.11(55.55-72.22)	<0.001	70 (60-75.83)	60 (53.33-66.66)	<0.001

School-age (n=33)						
Physical well-being	90 (80-90)	75 (60-80)	<0.001	90 (80-90)	70 (65-80)	<0.001
Emotional well-being	95 (90-95)	85 (70-85)	<0.001	90 (85-95)	80 (80-87.50)	<0.001
Self-esteem	100 (87.5-100)	80 (65-85)	<0.001	100 (85-100)	80 (75-80)	<0.001
Family	75 (70-77.50)	70 (60-80)	0.523	90 (80-95)	80 (70-85)	<0.001
Friends	100 (95-100)	80 (72.50-90)	<0.001	100 (87.50-100)	85 (72.50-92.50)	<0.001
School	75 (70-80)	70 (65-75)	0.014	90 (82.50-95)	80 (70-85)	<0.001
Total	90 (85.41-92.50)	76.66 (67.50-80.83)	<0.001	90.83 (87.50-95)	77.50 (70.83-83.33)	<0.001
Disease perception	73.33 (66.66-81.66)	63.33 (53.33-73.33)	<0.001	73.33 (66.66-76.66)	63.33 (55-75)	0.002

Data are presented as median (interquartile range). QoL: Quality of Life.*Significant p values are in bold.

Table 3. The impact of experiencing ADR on the QoL in terms of the preschool-age patient and the parent

Preschool-age (n=92)	Child self-reported		Parent proxy-reported	
	OR (95% CI)	p	OR (95% CI)	p
Model I (Physical wellbeing)				
ADRs (vs. no ADRs)	1.39 (0.58 – 3.30)	0.455	1.49 (0.60 – 3.69)	0.390
Female (vs. male)	0.82 (0.35- 1.94)	0.661	1.86 (0.74 – 4.66)	0.187
Age	1.34 (0.92 – 1.95)	0.125	1.81 (1.20 – 2.74)	0.005
Model II (Emotional well-being)				
ADRs (vs. no ADRs)	1.01 (0.40 - 2.50)	0.981	1.23 (0.518 – 2.91)	0.639
Female (vs. male)	1.36 (0.55 – 3.36)	0.506	1.17 (0.50 – 2.75)	0.714
Age	1.68 (1.12 – 2.25)	0.012	1.38 (0.95 – 2.01)	0.085
Model III (Self-esteem)				
ADRs (vs. no ADRs)	3.00 (0.97- 9.26)	0.055	3.15 (1.30 – 7.65)	0.011
Female (vs. male)	3.59 (1.23 – 10.45)	0.019	1.06 (0.43 – 2.58)	0.889
Age	2.17 (1.43 - 3.51)	0.002	1.23 (0.84 – 1.81)	0.277
Model IV (Family)				
ADRs (vs. no ADRs)	4.05 (1.44 – 11.37)	0.008	3.56 (1.43 - 8.82)	0.006
Female (vs. male)	1.82 (0.69 – 4.80)	0.221	0.76 (0.31 - 1.88)	0.560
Age	1.84 (1.20 - 2.83)	0.005	1.47 (0.98 - 2.20)	0.057
Model V (Friends)				
ADRs (vs. no ADRs)	2.33 (0.83 – 6.50)	0.106	2.23 (0.93 – 5.35)	0.070
Female (vs. male)	1.53 (0.57 – 4.11)	0.391	0.79 (0.33 – 1.88)	0.606
Age	2.28 (1.44 – 3.59)	<0.001	1.25 (0.85 – 1.82)	0.244

Model VI (School)				
ADRs (vs. no ADRs)	4.66 (0.98 – 22.09)	0.052	0.79 (0.185 - 3.44)	0.762
Female (vs. male)	2.91 (0.59 – 14.21)	0.185	0.48 (0.11- 2.07)	0.333
Age	2.40 (1.07-5.37)	0.032	0.66 (0.31 - 1.42)	0.296
Model VII (Other important issues)				
ADRs (vs. no ADRs)	-	-	12.56 (3.35 – 47.00)	<0.001
Female (vs. male)			1.49 (0.53 – 4.14)	0.443
Age			1.53 (0.99 – 2.37)	0.051
Model VIII (Disease perception)				
ADRs (vs. no ADRs)	1.16 (0.48 – 2.79)	0.726	2.38 (0.99 – 5.70)	0.052
Female (vs. male)	0.96 (0.409 – 2.29)	0.943	0.76 (0.32 – 1.80)	0.542
Age	1.53 (1.04 – 2.25)	0.029	1.15 (0.79 – 1.67)	0.450
Model IX (Total)				
ADRs (vs. no ADRs)	2.66 (1.01-7.04)	0.048	3.52 (1.36 – 9.12)	0.010
Female (vs. male)	1.90 (0.73- 4.92)	0.182	1.36 (0.54 – 3.39)	0.510
Age	2.05 (1.34- 3.16)	0.001	1.58 (1.06 – 2.36)	0.024

Table 4. *The impact of experiencing ADR on the QoL in terms of the school-age patient and the parent*

School-age (n=33)	Child self-reported		Parent proxy-reported	
	OR (95% CI)	p	OR (95% CI)	P
Model I (Physical well-being)				
ADRs (vs. no ADRs)	3.38 (0.65 – 17.48)	0.146	0.87 (0.12 – 6.09)	0.891
Female (vs. male)	2.68 (0.50 – 14.18)	0.245	20.17 (2.94 – 138.19)	0.002
Age	0.94 (0.66 – 1.33)	0.737	0.97 (0.67 – 1.40)	0.877
Model II (Emotional well-being)				
ADRs (vs. no ADRs)	7.33 (1.22 – 43.74)	0.029	0.46 (0.07 – 2.95)	0.419
Female (vs. male)	6.01 (0.94 – 38.20)	0.057	8.43 (1.38 – 51.19)	0.021
Age	0.85 (0.57 – 1.25)	0.409	1.26 (0.85 – 1.88)	0.236
Model III (Self-esteem)				
ADRs (vs. no ADRs)	2.20 (0.47 – 10.23)	0.314	9.83 (1.54 – 62.76)	0.016
Female (vs. male)	1.56 (0.33 – 7.25)	0.567	0.39 (0.06 – 2.46)	0.323
Age	1.05 (0.76 – 1.46)	0.732	1.32 (0.86 – 2.03)	0.193
Model IV (Family)				
ADRs (vs. no ADRs)	16.86 (1.75 – 162.26)	0.014	2.44 (0.53 – 11.31)	0.252
Female (vs. male)	1.41 (0.23 – 8.64)	0.710	0.76 (0.16 – 3.50)	0.730
Age	0.92 (0.67 – 1.27)	0.642	1.07 (0.80 – 1.45)	0.614
Model V (Friends)				
ADRs (vs. no ADRs)	1.79 (0.35 – 9.16)	0.481	6.40 (1.22 – 33.40)	0.028
Female (vs. male)	2.79 (0.56 – 13.93)	0.210	1.98 (0.39 – 10.02)	0.409
Age	1.14 (0.77 – 1.70)	0.495	1.02 (0.73 – 1.43)	0.872
Model VI (School)				

ADRs (vs. no ADRs)	2.81 (0.45 – 17.35)	0.265	1.01 (0.20 – 5.00)	0.987
Female (vs. male)	1.32 (0.24 – 7.22)	0.749	3.31 (0.69 – 15.87)	0.134
Age	1.04 (0.77 – 1.41)	0.770	1.09 (0.78 – 1.53)	0.599
Model VII (Disease perception)				
ADRs (vs. no ADRs)	1.57 (0.35 – 7.02)	0.555	1.17 (0.26 – 5.19)	0.836
Female (vs. male)	1.10 (0.24 – 4.89)	0.901	0.77 (0.17 – 3.41)	0.737
Age	1.04 (0.77 – 1.39)	0.788	1.07 (0.80 – 1.43)	0.611
Model VIII (Total)				
ADRs (vs. no ADRs)	5.95 (1.22 – 28.95)	0.027	6.43 (1.22 – 33.67)	0.027
Female (vs. male)	3.60 (0.66 – 19.37)	0.136	1.94 (0.38 – 9.78)	0.421
Age	0.95 (0.65 – 1.37)	0.790	1.05 (0.75 – 1.49)	0.742

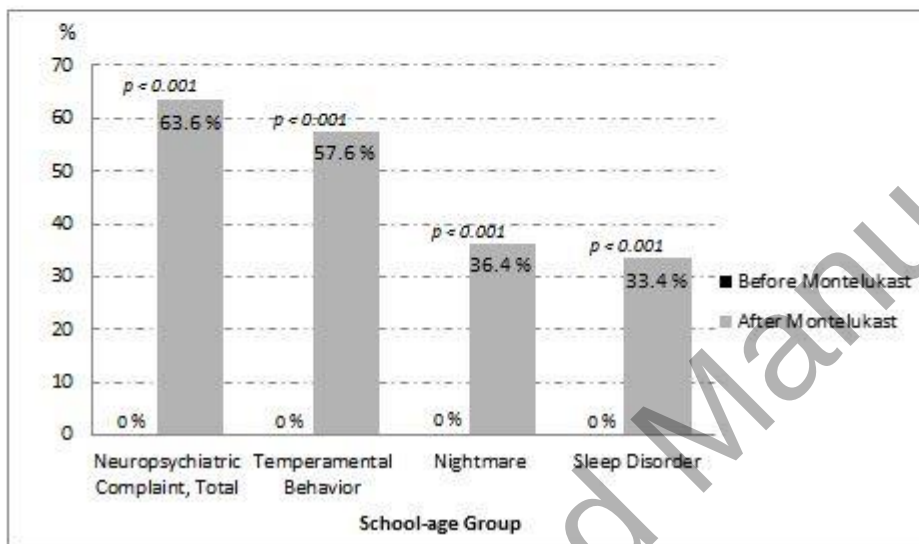
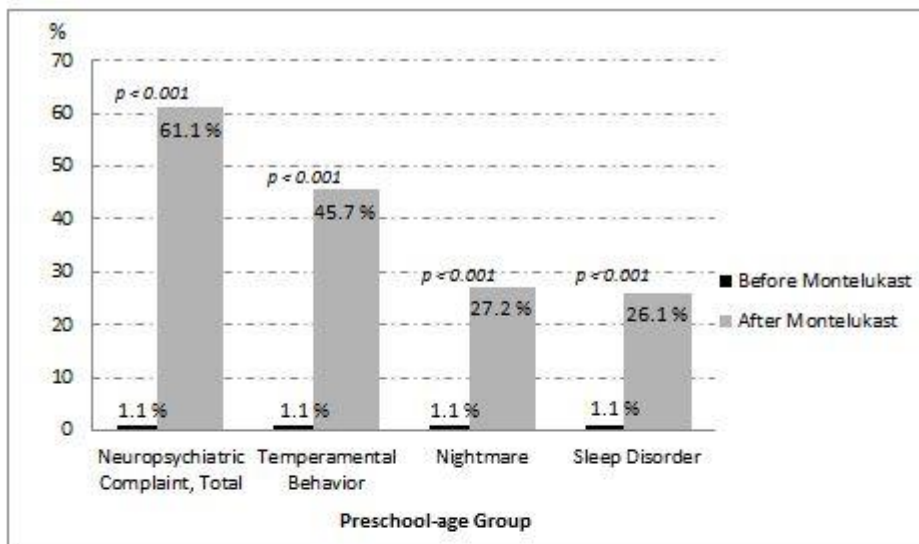


Figure. Comparison of pre-treatment and post-treatment development of neuropsychiatric complaint in preschool-age and school-age groups.

*The percentage of patients developing ADR are given in the neuropsychiatric complaint, total bar.