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QUETIAPINE USE BEFORE EIGHTEEN YEARS OF AGE AMONG FORMER ADOLESCENT PSYCHIATRIC INPATIENTS IN NORTHERN FINLAND

ABSTRACT

The use of antipsychotics among children and adolescents has increased in Finland, as it has worldwide. Quetiapine is the second most common antipsychotic prescribed to children and adolescents in Finland, after risperidone. Unlike risperidone, quetiapine has no licensed indication for use in children or adolescents. We examined indications for the prescription of quetiapine to adolescent psychiatric inpatients aged under 18 years.

The data covers a clinical sample of 508 adolescents, who were admitted for psychiatric inpatient treatment, between the ages 13–17 years, from April 2001 to March 2006. The psychiatric diagnoses leading to quetiapine prescription were searched from national healthcare registers, provided by the Finnish National Institute for Health and Welfare. The information on purchases of quetiapine, and other psychotropic medications, was obtained from the national register of prescribed medicines, provided by the Social Insurance Institution of Finland.

Of the 49 adolescents who had purchased quetiapine before 18 years of age, a total of 32 (65.3%) had an indication for psychotic disorder and 5 (10.2%) for an affective disorder. A total of 12 (24.5%) were defined as being off-label users of quetiapine. Two-thirds of adolescents defined as off-label users of quetiapine had been diagnosed with conduct disorder during index hospitalization. In addition, they were often impulsive, had suicidal behaviour or behavioural instability.

The prescription trends of quetiapine in youngsters mainly followed the official indications for quetiapine in adults. This symptomatic use of quetiapine is explained by a belief that it is both less addictive than benzodiazepines and has a lowering impact on suicidal behaviour.

KEYWORDS: ADOLESCENT, OFF-LABEL, PSYCHIATRIC INPATIENT, QUETIAPINE

INTRODUCTION

Antipsychotic use among children and adolescents has increased in the past ten years in Finland, as it has in many other Western countries such as the United States, Canada and Denmark (1-5). In Finland, very few antipsychotics are licensed for use in children (1). After risperidone, quetiapine is the second most commonly prescribed antipsychotic used for children and adolescents in Finland (6). In 2015, only 11% of those under 18 years of age who were prescribed an antipsychotic suffered from psychosis or bipolar disorder that included psychotic symptoms. Most of the antipsychotic prescriptions were dispensed off-label. The percentage of antipsychotic users who suffer from psychosis has gradually decreased since 2008, when 19% of the under 17-year-old users of antipsychotics were prescribed reimbursable medications, indicating that they suffered from a psychotic disorder (6).

Antipsychotics should always be prescribed with caution in children and adolescents and the duration of use should be kept to a minimum, because they may be at higher risk of experiencing side effects compared to adults (6,7). Different studies have proposed that antipsychotics may cause more severe hyperprolactinaemia in adolescents, and that minors may be at higher risk of significant weight gain and glucose and lipid abnormalities associated with atypical antipsychotics, compared to adult populations (7-9). Antipsychotics also increase the risk of neurological side effects in paediatric populations (10). Because of this, young patients should always be closely monitored for the development of these adverse side effects. Only a few studies have systematically monitored the short- and long-term safety of atypical antipsychotics in children and adolescents (9). Quetiapine is not recommended for first-line treatment in children and adolescents, because of the lack of detailed information on its use in this age group (6).

Quetiapine is an atypical antipsychotic which, in Finland, is licensed for use among adults in the treatment of schizophrenia and bipolar disorder, and as an adjunct in severe depression when antidepressant monotherapy has only had a partial impact (11, 12). A systematic review, involving pharmacoepidemiological studies between 2000 and 2015, concluded that quetiapine was the most frequently prescribed antipsychotic among adults for anxiety and insomnia (13). Off-label prescribing consisted of 40–75% of all antipsychotic prescriptions in the adult group and 36–93% in the children's group. Apart from anxiety and insomnia, adults were prescribed antipsychotics for mood disorders and agitation. Children were prescribed antipsychotics for attention-deficit hyperactivity disorder, anxiety or mood disorders (13).

Quetiapine is not licensed for use in minors in Finland, unlike risperidone, which is one of the few antipsychotics to have a license for use in children (1). However, in clinical practice quetiapine is used to treat various psychiatric symptoms in children and adolescents. The aim of this study is to investigate the use of quetiapine among adolescents with severe mental disorders. The study population consisted of a group of young psychiatric inpatients, whose psychiatric treatment episodes after discharge, and use of quetiapine, were followed until the age of eighteen years by linking the data to the information from national healthcare registers.

METHODS

STUDY POPULATION

This study is a part of the STUDY-70 project, which is a clinical study initiated in 2001 to examine the associations of several psychosocial risk factors with different psychiatric disorders. The study population consists of 508 minors (208; 40.9% male and 300; 59.1% female), who were admitted to psychiatric Unit 70 at Oulu University Hospital between April 2001 and March 2006 (referred to here as index hospitalization). Unit 70 treats all 13- to 17-year-old adolescents in need of acute psychiatric hospitalization in Northern Finland. The patients who were 18 years or older, had a diagnosis of a mental retardation, had an organic brain disorder or whose inpatient stay was too short for their interviews to be completed were excluded from the study population. 83.7% of the eligible adolescents (n=607) participated in the study. The study protocol was approved by the Ethics Committee of Oulu University Hospital.

RESEARCH INSTRUMENTS

To evaluate DSM-IV psychiatric disorders, all adolescent inpatients were interviewed during their hospitalization using the semi-structured Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime (K-SADS-PL) (14). Details from the parents' or guardians' K-SADS-PL interviews were used to complete information missing from the adolescents´ interviews. The interviews were conducted by the treating physician or by trained medical students.

NATIONAL REGISTERS

To explore the possible diagnoses that led to quetiapine prescriptions, we used the Care Register for Health Care (CRHC) (15), provided by the Finnish National Institute for Health and Welfare (THL). Details of outpatient admissions for specialized-level care were available from 1998 to the end of 2016. Diagnoses in CRHC were based on ICD-9 classification before 1996, and on ICD-10 classifications from 1996 onwards (15).

Information about quetiapine and other psychotropic medicine purchases (ATC: N02-, N03-, N05-, N06- and N07B-) among the study population was obtained from the Social Insurance Institution (SII) of Finland. The information of purchases was available from 1999 to the end of 2012 (16).

QUETIAPINE PURCHASES

From the study population, we identified those adolescents who had purchased quetiapine before the age of 18 (n=49). Both the number of quetiapine purchases and the age at first purchase were obtained from the SII of Finland. SII also provided information on whether a patient had bought other psychotropic drugs before quetiapine. From the CRHC, we searched diagnoses for psychotic disorders before quetiapine purchase. If a patient did not have a diagnosis, we selected the psychiatric diagnosis the patient had prior to their purchase of quetiapine (purchase-related diagnosis). We grouped the patients into three different indication groups according to the diagnoses they had prior to purchasing quetiapine: psychotic disorder, affective disorder and off-label. This grouping was based on adult official licensing for quetiapine use in Finland, although all usage is "off-label" among minors.

The psychotic disorder group (n=32) consists of patients with the following diagnoses: F20, F25 (Schizophrenia spectrum disorders, n=6), F22 (Delusional disorders, n=2), F21 (Schizotypal disorders, n=2), F23 (Brief psychotic disorder, n=3), F28 (Other specific psychotic disorder, n=2), F29 (Unspecified or other psychotic disorder, n=14), F31.2 (Bipolar disorder, current episode manic severe with psychotic features, n=2) and F32.3 (Major depressive disorder, severe with psychotic features, n=1). In the affective disorder group (n=5), patients with following diagnoses were included: F31.9 (Bipolar disorder, unspecified, n=2) and F32.2 (Major depressive disorder, single episode, severe without psychotic features, n=3). The Off-label group (n=12) contains patients with the following diagnoses: F32.1 (Major depressive disorder, single episode, moderate, n=3), F41.2 (Mixed anxiety and depressive disorder, n=1), F41.9 (Anxiety disorder, unspecified, n=1), F43.1 (Post-traumatic stress disorder (PTSD), n=1), F84.8 (Other pervasive developmental disorder, n=1), F92.0 (Depressive conduct disorder, n=2), F93.8 (Other childhood emotional disorders, n=1), F98.0 (Non-organic enuresis, n=1) and F98.8 (Other specified behavioural and emotional disorders with onset usually occurring in childhood and adolescence, n=1).

CLINICAL CHARACTERISTICS DURING ADOLESCENTS' INDEX HOSPITALIZATION

Reasons for index hospitalization were based on the information gathered using the semi-structured admission form at admission to psychiatric unit 70. Index diagnoses are those DSM-IV diagnoses that the patients fulfilled in the K-SADS-PL interviews during index hospitalization. Multiple diagnoses for one patient were possible (17).

Information on non-suicidal self-injury (NSSI), suicidal ideation and suicide attempt was based on the items in the screening section for depressive disorders in the K-SADS-PL interview. In this study NSSI, suicidal ideation and suicide attempt were defined as being present if the threshold level of an item was met. Any self-damaging act without the intent to die that had occurred at least 4 times a year or caused serious injury to self, met the threshold criterion for NSSI. Those adolescents who were classified as having suicidal ideation, had planned the method of suicide and had recurrent suicidal thoughts. The threshold criterion for suicide attempt was achieved if the adolescent had recently harmed her- or himself with the intention of dying or the self-harm had been life-threatening.

Impulsivity in adolescence was defined based on one question derived from the screening section in the K-SADS-PL interview. An adolescent was asked whether they had ever, during their lifetime, often acted before thinking and if there had ever been a time when this kind of behaviour caused trouble. In this study, the threshold value for impulsivity was met if the adolescent was often impulsive and the problem had a moderate to severe effect on functioning.

K-SADS-PL interview also provided information about the adolescents' family structure/living environment prior to index hospitalization. Four family structure subgroups were created, based on the interview information: two biological parents, one biological parent with or without married/cohabiting partner, child welfare placement and other (alone, residential home or foster family). Other covariates in this study, obtained from the K-SADS-PL interview, included

adverse life-events including: witnessing domestic violence (yes/no), physical abuse by parents (yes/no) and victim of sexual abuse (yes/no).

FOLLOW-UP INFORMATION

Diagnoses for personality disorders (ICD-9: 301, ICD-10: F60), after the index hospitalization period until the end of 2012, were based on in- and outpatient information obtained from the CRHC and reviewed according to the DSM-IV-TR criteria by an experienced psychiatrist (LK). The validation of personality disorders has been described in more detail earlier (18).

STATISTICAL METHODS

Group difference in categorical variables was examined with Pearson Chi-square or Fisher's Exact test and, in continuous variables, using Student's t-test. All statistical tests were two-tailed and a limit for statistical significance was set at $p<0.05$. Statistical analyses were performed using IBM SPSS version 23 for Windows.

RESULTS

Of the 49 adolescents who had used quetiapine by the age of 18, 32 (65.3%) had received a diagnosis of psychotic disorder and 5 (10.2%) a diagnosis of affective disorder before their first quetiapine purchase. A total of 12 (24.5%) were defined as being off-label users of quetiapine, according to the official indications for quetiapine use in adults.

Table 1 shows the adolescence-related sociodemographic and clinical characteristics of the study subjects by three different indication groups. Age (in years) at first quetiapine purchase did not differ between indication groups for psychotic disorder (mean=15.8, SD=1.3), affective disorder (16.2, 0.8) and off-label (15.7, 1.1) (p=0.708).

In the psychotic disorder indication group, 56.3% of the adolescents had fulfilled the DSM-IV criteria for that disorder during their index hospitalization (p=0.001). Further, affective disorder during index hospitalization was the most common diagnosis, both in the affective disorder indication group (80.0%) and among off-label users of quetiapine (75.0%) (p=0.007). The great majority of off-label users (66.7%) had been diagnosed with conduct disorder during index hospitalization (p=0.026). Half of the off-label users displayed impulsivity during index hospitalization (p=0.001).

Figure 1 demonstrates the use of psychotropic medication before first quetiapine purchase by the study groups. There was no statistically significant difference between the three indication groups for quetiapine in the preceding use of mood stabilizers (p=0.492), antipsychotics (p=0.754), antidepressants (p=0.052) and other psychotropic medication (p=0.132) as well as among those without any previous psychotropic medication (p=0.163). Of note, however, is that most patients in the affective disorder indication group (80.0%) had used antidepressants prior to their first purchase of quetiapine.

Table 2 presents the case characteristics of those study subjects defined as being off-label users of quetiapine. Only three of the off-label quetiapine users had psychotic symptoms as a reason for adolescent psychiatric admission, and only one fulfilled the diagnostic criteria for psychotic disorder. NSSI, suicidal behaviour and impulsivity were common among off-label users. One third of the off-label users was diagnosed with personality disorder later in life, all being women.

Table 1. Sociodemographic and clinical characteristics of study subjects assessed during their psychiatric inpatient hospitalization at ages 13–17 years in relation to quetiapine use before 18 years of age.

	Indication group for quetiapine prescription				
	Psychotic disorder (n=32)	Affective disorder (n=5)	Off-label (n=12)	Total (n=49)	P-value
Male gender, n (%)	13 (40.6)	1 (12.5)	5 (41.7)	19 (38.8)	0.814
Age at admission. mean (SD)	15.1 (1.3)	15.0 (1.4)	14.9 (1.3)	15.0 (1.3)	0.949
Family type, n (%)					
Two biological parents	14 (43.8)	3 (60.0)	3 (25.0)	20 (40.8)	0.364
One biological parent	5 (15.6)	1 (20.0)	3 (25.0)	9 (18.4)	0.746
Child welfare placement	8 (25.1)	1 (20.0)	5 (41.7)	14 (28.6)	0.497
Other type of home environment	5 (15.6)	0 (0)	1 (8.3)	6 (12.2)	1.000
Psychiatric disorders in adolescence, n (%)					
Psychotic disorder	18 (56.3)	1 (20.0)	0 (0.0)	19 (38.8)	0.001
Anxiety disorder	5 (15.6)	2 (40.0)	3 (25.0)	10 (20.4)	0.304
Affective disorder	10 (31.3)	4 (80.0)	9 (75.0)	23 (46.9)	0.007
Conduct disorders	11 (34.4)	0 (0)	8 (66.7)	19 (38.8)	0.026
Substance use disorders	11 (34.4)	1 (20.0)	5 (41.7)	17 (34.7)	0.816
Any personality disorder (PD)*, n (%)	5 (15.6)	3 (60.0)	4 (33.3)	12 (24.5)	0.071
Schizotypal PD	0 (0)	1 (20.0)	0 (0)	1 (2.0)	0.102
Borderline PD	3 (9.4)	2 (40.0)	3 (25.0)	8 (16.3)	0.114
Other PD	2 (6.3)	0 (0)	1 (8.3)	3 (6.1)	1.000
Suicidal behaviour, n (%)					
Suicide ideation	16 (50.0)	3 (60.0)	7 (58.3)	26 (53.1)	0.910
Suicide attempt	6 (18.8)	1 (20.0)	4 (33.3)	11 (22.4)	0.674
Non-suicidal self-injury	14 (43.8)	2 (40.0)	6 (50.0)	22 (44.9)	0.910
Impulsivity, n (%)	1 (3.1)	1 (20.0)	6 (50.0)	8 (16.3)	0.001
Witness to domestic violence, n (%)	11 (34.4)	2 (40.0)	7 (58.3)	20 (40.8)	0.327
Victim of physical abuse, n (%)	6 (18.8)	0 (0.0)	5 (41.7)	11 (22.4)	0.143
Victim of sexual abuse, n (%)	8 (25.0)	1 (20.0)	2 (16.7)	11 (22.4)	0.873

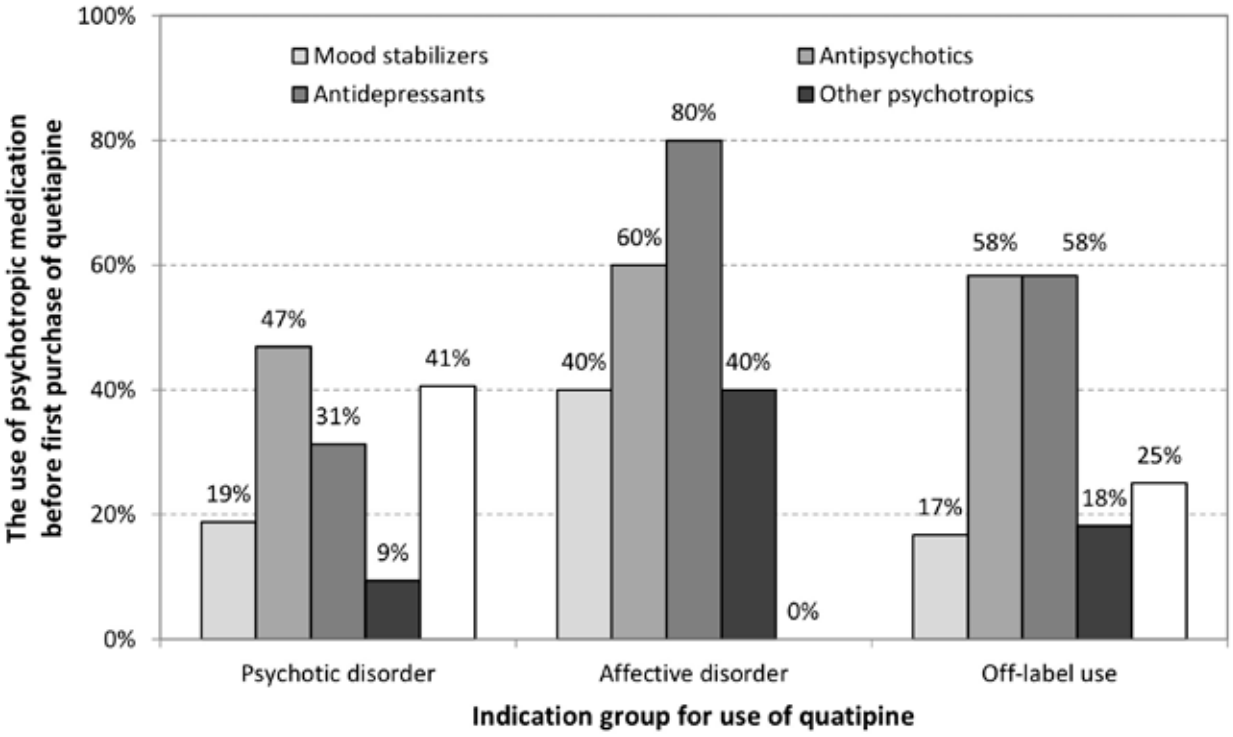
* Personality disorders at age 16 or above, follow-up information. Other PD includes other specific PD (F60.8) and PD nos (F60.9)

Table 2. Case characteristic of the study subjects defined as being off-label users of quetiapine.

id	First purchase of quetiapine		Characteristics assessed during index hospitalization between the ages 13-17 years				Personality disorder (PD) at age 16 or above
	Age, sex	Purchase-related psychiatric disorder	Reason for admission	Psychiatric disorders	Suicidal behaviour	Impulsivity	
1	16, F		Depressive and psychotic symptoms, substance use	MDD (single episode, moderate), Cannabis and alcohol abuse	Suicide ideation	Present	Borderline PD at age 21 years
2	16, F	MDD (single episode, moderate)	Suicidality, NSSI	MDD (single episode, moderate)	NSSI, suicide ideation	Present	No
3	17, M		Suicidality, anxiety, behavioural problems	Depressive conduct disorder	NSSI, suicide attempt	Present	No
4	16, M	Mixed anxiety and depressive disorder	Anxiety	Conduct disorder (adolescent-onset type), Cannabis dependence, Opioid abuse	None	Not present	No
5	16, F	Anxiety disorder (unspecified)	Depressive symptoms	Childhood emotional disorder, MDD (single episode, moderate)	NSSI, suicide ideation	Not Present	No
6	15, F	PTSD	Suicidality, anxiety	Generalized anxiety disorder in childhood, PTSD	NSSI, suicide attempt	Not present	Bordeline PD at age 22 years
7	13, M	Other pervasive developmental disorder	Not reported	Conduct disorder (adolescent-onset type), MDD (single episode, unspecified), Tourette's disorder	None	Not present	No
8	17, F	Depressive conduct disorder	Psychotic symptoms	Depressive conduct disorder, Social phobia, Other specified behavioural and emotional disorders (onset in childhood and adolescence)	NSSI, suicide attempt	Present	PD nos at age 27 years
9	16, M		Depressive symptoms, behavioural problems	Conduct disorder (adolescent-onset type)	None	Not Present	No
10	16, F	Childhood emotional disorder	Psychotic symptoms, problems at school	MDD (single episode, unspecified), Childhood emotional disorder	None	Not Present	No
11	15, M	Non-organic enuresis	Behavioural problems	ADHD, Non-organic enuresis	None	Present	No
12	15 F	Other specified behavioural and emotional disorder (onset in childhood and adolescence)	Suspected to have a severe mental disorder	Schizoaffective disorder	NSSI, suicide attempt	Present	Borderline PD at age 21 years

M = Male. F = Female. NSSI = Non-Suicidal Self-Injury. MDD = Major depressive disorder. ADHD = Attention-Deficit Hyperactivity Disorder. PTSD = Post-traumatic stress disorder

Figure 1. The use of psychotropic medication before the first purchase of quetiapine, by indication groups.



DISCUSSION

A major finding in our study of former adolescent psychiatric inpatients was that most prescriptions of quetiapine to adolescents aged under 18 were given in accordance with the licensed indications for its use in adults, and only one fourth of prescriptions were used off-label. In a Norwegian study that covered all prescriptions in the entire Norwegian population, except those given in institutions, the most common diagnoses among 0–18-year-old male quetiapine users were hyperkinetic disorder (44.6%), anxiety disorder (28.5%) and depressive illness (25.3%), and in girls, anxiety disorder (57.1%), depressive illness (52.4%) and schizophrenia-like psychosis (29.3%) (19). These results are in line with our findings, with exception of hyperkinetic disorder. Additionally, in our study population, a notably high number (66%) of adolescents in the off-label indication group were diagnosed with conduct disorder during their index hospitalization. Only 11% of Finnish children and adolescents using antipsychotics were reported as suffering from a psychotic disorder or bipolar disorder that included psychotic symptoms and had, therefore, justified indications for their medication (6). In that study, however, only the overall use of antipsychotics was analysed, while in our study we focused on quetiapine, which was prescribed in accordance with adult indications among 75% of the adolescents.

In our study population, more than half of the patients in the affective disorder indication group, and one third of the patients in the off-label indication group were diagnosed with a personality disorder after they turned 16. Furthermore, 67% of all quetiapine users with a personality disorder suffered from borderline personality disorder.

We suggest that adolescent patients with a developing personality disorder may be prescribed quetiapine even before they are given a diagnosis. We believe this is because antipsychotics are frequently used in the management of mood instability in patients with borderline personality disorder, and not just for psychotic symptoms (20). Patients with borderline personality disorder may also suffer from brief psychotic reactions (21), which may justify antipsychotic medication use. Additionally, quetiapine may possess potential benefits as a suicide risk-reducing drug among impulsive youths who are developing borderline personality disorder (22).

Another finding in our study was that a notable number of adolescents in the off-label group were diagnosed as suffering from an affective disorder or/and conduct disorder during their index hospitalization. The off-label group was also characterized by impulsivity and suicidal behaviour in adolescence. In the treatment of young patients, psychotropic medications are targeted to specific disorders or for controlling different symptoms of mood and behavioural instability, such as aggression, impulsiveness, fears and self-injurious behaviour (23). This is in line with our study results, since 50% of patients in our off-label indication group were impulsive and 7 out of 12 had a history of suicidal behaviour.

A strength of our study is that details of psychotropic medicine purchases were extracted from the national register of purchase of medicines. The Care Register of Health Care provided us with detailed information on the adolescents' psychiatric treatment periods, covering the whole lifespan of the study subjects (24,25). During index hospitalization, between the ages 13–17 years, adolescents' psychiatric disorders were carefully determined using the semi-structured diagnostic K-SADS-PL interview, which has been shown to have good psychometric properties for screening DSM-IV diagnoses in adolescents (14).

A limitation of our study is that all of the adolescents in this study were psychiatric inpatients, so the results could differ in adolescents treated in outpatient care. Our data did not include information on the patients' sleep disturbances, which we see as a weakness of the study, because quetiapine is commonly prescribed to children and adolescents for this condition, in order to avoid benzodiazepine use. A further weakness of our approach is that the definition of diagnoses for quetiapine purchases in the off-label group were assumed to be the diagnoses just before the purchase in the CRHC, because we did not have access to the patients' medical records.

In conclusion, compared to the findings in previous literature, our study confirms that quetiapine prescriptions for youngsters are made in accordance with the treatment practices used for adults. Those children and adolescents who are prescribed quetiapine off-label were often impulsive, had demonstrated suicidal behaviour or were behaviourally unstable. We believe that this symptomatic use of quetiapine is explained by the fact that it is believed to be less addictive than benzodiazepines and to have a lowering impact on suicide risk.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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