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Off-Label Psychotropic Prescribing in Children and Adolescents: Prevalence and Associated Factors in a Moroccan Child and Adolescent Psychiatry Department

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Abstract **Original Research Article**

Background: Off-label prescribing of psychotropic medications is common in child and adolescent psychiatry because of the limited number of drugs approved for pediatric use. However, data from North Africa remain scarce. This study aimed to estimate the prevalence of off-label psychotropic prescribing in a Moroccan child and adolescent psychiatry department and to identify the clinical and therapeutic factors associated with this practice. ***Methods:*** We conducted a retrospective observational study in the Child and Adolescent Psychiatry Department of Ar-Razi University Psychiatric Hospital (Salé, Morocco). Medical records and prescriptions issued between May and July 2026 were reviewed. Off-label status was determined according to U.S. Food and Drug Administration (FDA) labeling with regard to indication, age, dosage, route of administration, and contraindications. Descriptive analyses were performed, and associations between off-label prescribing and demographic or clinical variables were assessed using Pearson's chi-square test or Fisher's exact test, with the Mann– Whitney test used for continuous age comparisons. ***Results:*** A total of 112 patients (mean age 13.2 ± 3.9 years; 54.5% male) were included. Overall, 52.7% (95% CI: 43.5–61.7) of patients received at least one off-label psychotropic prescription. Off-label prescribing occurred in 32.1% (95% CI: 24.2–41.3) of first-line psychotropics and 77.8% (95% CI: 61.9–88.3) of second-line psychotropics. Nearly all offlabel prescriptions were related to non-approved indications. Anxiety disorders (100%) and attention-deficit/hyperactivity disorder (78.9%) showed the highest proportions of off-label prescribing. All clonidine prescriptions and 50% of sertraline prescriptions were off-label, whereas off-label use was uncommon for risperidone (3.7%) and fluoxetine (19.4%). Younger age, primary diagnosis, and prescribed molecule were significantly associated with off-label prescribing (all $p < 0.05$), whereas sex was not. ***Conclusions:*** Off-label prescribing of psychotropic medications is highly prevalent in this Moroccan child and adolescent psychiatry setting, particularly for second-line treatments. The observed pattern appears to reflect limited therapeutic availability and regulatory constraints rather than inappropriate prescribing practices. These findings highlight the need for national guidance, improved access to evidence-based pediatric psychotropic medications, and larger multicenter studies to support safe and rational prescribing in low- and middle-income countries.

Keywords: off-label prescribing; psychotropic drugs; child psychiatry; adolescent psychiatry; pediatrics; Morocco; psychopharmacology; FDA.

1. INTRODUCTION

Mental disorders in children and adolescents constitute a major public health concern owing to their frequency, their impact on development, and their potential persistence into adulthood. [1,2] Management relies primarily on psychotherapeutic and psychosocial interventions, but psychotropic medications remain necessary in numerous clinical situations, particularly in attention-deficit/hyperactivity disorder (ADHD), depressive disorders, severe anxiety disorders, psychotic disorders, and bipolar disorder. [3,4] However, the limited number of medications holding a marketing authorization specifically for the pediatric population frequently leads to off-label prescribing, particularly in child and adolescent psychiatry. [5–7]

This practice is widely reported in the international literature and represents a major component of pediatric psychopharmacology, particularly for antidepressants and antipsychotics, whose approved indications in children remain limited.[7–9] However, an

off-label prescription should not be equated with inappropriate practice. When it is based on the best available scientific evidence, addresses a clinical need not covered by approved treatments, and is accompanied by an individualized benefit-risk assessment together with appropriate information and monitoring, it may constitute a practice consistent with professional recommendations.[5,10] Finally, the frequency of off-label prescribing varies according to the regulatory reference framework used, as approved indications, age limits, dosages, and conditions of use may differ between the FDA, the EMA, and national regulatory authorities. [6,11,12]

Off-label use refers to the use of a medication holding a marketing authorization, but under conditions that do not conform to that authorization (indication, age, dose, route of administration, or other approved condition of use). [13]

In Morocco, this issue is of particular importance given the limited number of approved pediatric indications and the restricted availability of certain therapeutic alternatives. Despite this, Moroccan data on the prevalence of off-label psychotropic prescribing in child and adolescent psychiatry remain scarce. The few available studies do not yet allow a precise description of the scale of the phenomenon or of the medications and clinical situations most concerned. To our knowledge, one of the main Moroccan studies published on this topic was conducted in the child and adolescent psychiatry department of the Ibn Rochd University Hospital Center in Casablanca.[14] This cross-sectional study, which included 64 patients and analyzed 186 prescription lines, reported that 44% of psychotropic prescriptions were off-label and that 40.6% of patients had received at least one off-label medication.[14] However, its singlecenter design and limited sample size did not allow an assessment of potential variations in practice across regions, institutions, and models of care organization in Morocco.

It is in this context that we conducted a retrospective study within the child and adolescent psychiatry department of the Ar-Razi University Psychiatric Hospital in Salé. The primary objective was to estimate the prevalence of off-label psychotropic prescribing in children and adolescents, using the FDA reference framework, and to identify the main clinical and therapeutic factors associated with this practice.

2. MATERIALS AND METHODS

2.1. Study design and setting

This was a retrospective observational study, with a descriptive and analytical design, conducted within the child and adolescent psychiatry department of the Ar-Razi University Psychiatric Hospital in Salé (Morocco).

2.2. Study period

The study was conducted between May and July 2026.

2.3. Study population

The study population comprised all children and adolescents who received care in the child and adolescent psychiatry department during the study period and for whom a prescription including at least one psychotropic medication was issued.

2.4. Inclusion criteria

The following were included in the study:

- prescriptions issued between May and July 2026 containing at least one psychotropic medication;
- patients aged 18 years or less, followed in the child and adolescent psychiatry department;
- available medical records allowing the collection of the necessary clinical information.

2.5. Exclusion criteria

Medical records that were incomplete or unavailable, precluding determination of the patient's diagnosis or demographic characteristics, were excluded from the study.

Of the 114 records initially identified, 2 were excluded owing to missing data. A total of 112 patients were included in the final analysis.

2.6. Data collection

Prescriptions were collected retrospectively from the prescriptions issued within the child and adolescent psychiatry department. For each prescription, the international nonproprietary name, therapeutic class, dosage, route of administration, and any concomitant second psychotropic medication were recorded.

Each prescription could include one or two psychotropic medications. The first and second psychotropic medications were analyzed separately; each being considered as a distinct therapeutic unit. For each of them, the prescribed molecule, the clinical indication, and the onlabel or off-label status were recorded.

2.7. Determination of off-label status

The on-label or off-label status of each prescription was determined by comparison with the indications, age ranges, dosages, and conditions of use specified in the U.S. Food and Drug Administration (FDA) prescribing information. A prescription was considered off-label whenever at least one of the following criteria differed from the FDA-approved conditions: indication, age range, dosage, route of administration, or contraindication.

2.8. Variables collected

Demographic characteristics (age and sex) as well as clinical data, including the diagnosis or diagnoses recorded in the medical file, the presence of psychiatric

comorbidities, personal and family history, educational level, and therapeutic strategy (monotherapy or combination therapy), were retrospectively collected from patient records.

2.9. Ethical considerations

This retrospective study relied exclusively on the review of data from medical records and prescriptions, without any intervention involving patients. Data were anonymized prior to analysis to preserve the confidentiality of personal information.

2.10. Statistical analysis

2.10.1. Software

Statistical analyses were performed using Python (version 3.10) with the Pandas, NumPy, and SciPy libraries. Tables and figures were produced using Matplotlib and OpenPyXL.

2.10.2. Description of data

Qualitative variables (sex, diagnosis, molecule, therapeutic class, off-label status, etc.) were described using frequencies (n) and percentages (%), calculated relative to the available data for each variable.

Quantitative variables (age) were described using the mean ± standard deviation and the median [range or interquartile range], according to the observed distribution. Age was also categorized into groups (< 6 years; 6-11 years; 12-18 years) for the purposes of certain comparative analyses.

2.10.3. Estimation of off-label prevalence

The prevalence of off-label prescribing was calculated separately for the first and second psychotropic medications of each prescription, as well as at the patient level (proportion of patients who received at least one off-label prescription among the recorded treatments). Ninety-five percent confidence intervals were calculated using the Wald method.

2.10.4. Statistical tests of association

The association between off-label status and categorical variables (sex, age group, primary diagnosis, prescribed molecule, therapeutic class) was assessed using Pearson's chi-square test on contingency tables.

When the expected cell count in at least one cell of the contingency table was below 5 (Cochran's rule), the chi-square test was replaced by Fisher's exact test for 2 × 2 tables. For higher-dimension contingency tables, categories with fewer than 5 observations were grouped under an "Other" category to limit the number of low-count cells.

Age, as a continuous variable, was additionally compared between the off-label and on-label prescription groups using the Mann-Whitney test, used to compare the age distributions between the two groups.

2.10.5. Significance threshold

The statistical significance threshold for all tests was set at $p < 0.05$. Any p-value below this threshold was considered to indicate a statistically significant association between the variable studied and off-label status.

3. RESULTS

3.1. Characteristics of the study population

The study population comprised 112 patients with a mean age of 13.2 ± 3.9 years. It was predominantly composed of adolescents, with 72.3% of patients aged 12 to 17 years, and showed a slight male predominance (54.5%). A psychiatric comorbidity was present in 61.6% of patients. The majority received a single psychotropic medication, while 32.1% received a combination of at least two psychotropic medications. The most common primary diagnoses were depressive disorder, autism spectrum disorder, and ADHD (Table 1).

Table 1: Demographic and clinical characteristics of the patients

Variable	n = 112
Age, mean ± SD (years)	13.2 ± 3.9
< 6 years	6 (5.4%)
6-11 years	25 (22.3%)
12-18 years	81 (72.3%)
Male sex	61 (54.5%)
Psychiatric comorbidity	69 (61.6%)
School attendance	87 (77.7%)
Monotherapy (1 psychotropic medication)	76 (67.9%)
Combination therapy (≥ 2 psychotropic medications)	36 (32.1%)
Primary diagnosis	
Depressive disorder	34 (30.4%)
Autism spectrum disorder	22 (19.6%)
ADHD	19 (17.0%)
Intellectual developmental disorder	8 (7.1%)
Psychotic disorder	8 (7.1%)

Anxiety disorder	7 (6.3%)
Obsessive-compulsive disorder	6 (5.4%)
Other	8 (7.1%)

3.2. Characteristics of psychotropic prescriptions

The first prescribed psychotropic medication most often belonged to the selective serotonin reuptake inhibitor (SSRI) class, followed by second-generation antipsychotics and alpha-2 adrenergic agonists. When a second psychotropic medication was prescribed, hypnotics and second-generation antipsychotics predominated. The most frequently prescribed molecules as the first psychotropic medication were fluoxetine, risperidone, and clonidine (Table 2).

Table 2: Molecules and therapeutic classes prescribed, first and second psychotropic medication

Molecule	Class	First medication n (%)	Second medication n (%)
Fluoxetine	SSRI	31 (27.7%)	2 (5.6%)
Sertraline	SSRI	14 (12.5%)	–
Escitalopram	SSRI	5 (4.5%)	–
Paroxetine	SSRI	1 (0.9%)	–
Risperidone	SGA	27 (24.1%)	4 (11.1%)
Olanzapine	SGA	4 (3.6%)	1 (2.8%)
Quetiapine	SGA	1 (0.9%)	8 (22.2%)
Molecule	**Class**	**First medication n (%)**	**Second medication n (%)**
Aripiprazole	SGA	4 (3.6%)	2 (5.6%)
Clonidine	Alpha-2 agonist	17 (15.2%)	–
Methylphenidate (immediate-release)	Psychostimulant	4 (3.6%)	–
Hydroxyzine	Anxiolytic	2 (1.8%)	5 (13.9%)
Melatonin	Hypnotic	2 (1.8%)	12 (33.3%)
Other (lamotrigine, lorazepam)	–	–	2 (5.6%)
Total		112	36

SGA: second-generation antipsychotic; SSRI: selective serotonin reuptake inhibitor.

3.3. Frequency of off-label prescribing

Among the 112 included patients, 59 had received at least one off-label prescription, corresponding to a patient-level prevalence of 52.7% (95% CI: 43.5–61.7). The proportion of off-label prescriptions was 32.1% (95% CI: 24.2–41.3) for the first psychotropic medication and 77.8% (95% CI: 61.9–88.3) for the second (Table 3). In almost all cases, off-label status was related to use for an indication not approved by the FDA.

Table 3: Prevalence of off-label prescribing.

Analysis	N	n off-label	% (95% CI)
First psychotropic medication	112	36	32.1 (24.2–41.3)
Second psychotropic medication	36	28	77.8 (61.9–88.3)
Patient level (≥ 1 off-label prescription)	112	59	52.7 (43.5–61.7)

3.4. Molecules and clinical indications involved

For the first psychotropic medication, the highest proportions of off-label prescriptions were observed in patients with anxiety disorder (100%) or ADHD (78.9%). No off-label prescriptions were found among patients with a psychotic disorder. All clonidine prescriptions and half of sertraline prescriptions were off-label, compared with 19.4% of fluoxetine prescriptions and 3.7% of risperidone prescriptions (Table 4).

For the second psychotropic medication, all prescriptions of melatonin, quetiapine, and aripiprazole were off-label. These results should be interpreted with caution given the small size of this subgroup (n = 36) (Supplementary Table S1).

3.5. Factors associated with off-label prescribing

In bivariate analysis, off-label status for the first psychotropic medication was significantly associated with age group ($p = 0.001$), primary diagnosis ($p < 0.001$), and prescribed molecule ($p < 0.001$), but not with sex ($p = 0.873$) (Table 4). Analysis of age as a continuous variable likewise showed a significantly lower mean age among patients receiving an off-label prescription than among those receiving an on-label prescription (11.7 ± 4.4 versus 13.9 ± 3.5 years; $p = 0.026$).

For the second psychotropic medication, only the association between the prescribed molecule and off-label status reached statistical significance ($p < 0.001$). No significant association was found with sex, age group, or primary diagnosis (Supplementary Table S1).

Table 4: Factors associated with off-label status of the first prescribed psychotropic medication

Variable	Off-label n (%)	On-label n (%)	p
Sex Female	16 (31.4%)	35 (68.6%)	0.873
Male	20 (32.8%)	41 (67.2%)	
Age group < 6 years	3 (50.0%)	3 (50.0%)	**0.001**
6-11 years	15 (60.0%)	10 (40.0%)	
12-18 years	18 (22.2%)	63 (77.8%)	
Primary diagnosis Psychotic disorder	0 (0.0%)	8 (100%)	**< 0.001**
Depressive disorder	6 (17.6%)	28 (82.4%)	
ADHD	15 (78.9%)	4 (21.1%)	
IDD	1 (12.5%)	7 (87.5%)	
Anxiety disorder	7 (100%)	0 (0.0%)	
ASD	6 (27.3%)	16 (72.7%)	
Molecule Aripiprazole	0 (0.0%)	4 (100%)	**< 0.001**
Clonidine	17 (100%)	0 (0.0%)	
Escitalopram	0 (0.0%)	5 (100%)	
Fluoxetine	6 (19.4%)	25 (80.6%)	
Methylphenidate	0 (0.0%)	4 (100%)	
Olanzapine	0 (0.0%)	4 (100%)	
Risperidone	1 (3.7%)	26 (96.3%)	
Sertraline	7 (50.0%)	7 (50.0%)	

Pearson's chi-square test; Fisher's exact test used for 2 × 2 comparisons with low expected cell counts. Obsessivecompulsive disorder (n = 6) and the "Other" category (n = 8) were excluded from the analysis by primary diagnosis; paroxetine (n = 1), hydroxyzine (n = 2), and melatonin (n = 2) were excluded from the analysis by molecule owing to insufficient sample sizes for statistical testing. Bold p-values indicate a statistically significant association (threshold 0.05). A complementary analysis of age as a continuous variable (Mann-Whitney test) confirmed this association (p = 0.026).

4. DISCUSSION

4.1. Main findings

This retrospective study, conducted in a Moroccan university hospital child and adolescent psychiatry department, revealed a high prevalence of off-label psychotropic prescribing in children and adolescents, with 52.7% of patients having received at least one off-label prescription according to the FDA reference framework. This prevalence differed markedly between the first (32.1%) and second (77.8%) prescribed psychotropic medications, and mainly concerned a small number of well-identified molecules (clonidine, sertraline, melatonin, quetiapine) and diagnoses (anxiety disorder, ADHD). Age, primary diagnosis, and prescribed molecule were significantly associated with off-label status, unlike sex. These findings, discussed below in light of the international literature, are broadly consistent with data reported in other countries, while revealing certain specificities likely related to the Moroccan regulatory and therapeutic context.

4.2. Comparison of overall prevalence with the literature

The prevalence of 52.7% of patients receiving at least one off-label prescription in our study lies at the upper end of the international range, yet remains consistent with several recent studies. In Morocco, Samouh et al., in a single-center cross-sectional study conducted at the Ibn Rochd University Hospital Center in Casablanca, reported a similar patient-level prevalence (40.6%) and a prescription-level prevalence of 44% [14], figures lower than ours but confirming the substantial frequency of this practice in the Moroccan context. In Norway, Rosland et al., in a nationwide study of all psychotropic prescriptions among individuals under 18 years of age, reported a markedly lower overall prevalence for most therapeutic classes[7]. Carton et al., in their systematic review covering several European countries, described highly heterogeneous prevalences, ranging from 20% to over 60% depending on the study, population, and reference framework used [9], which places our result at the higher, but not aberrant, end of this range. More recently, Taurines et al., in a prospective multicenter study conducted across 18 European child and adolescent psychiatry centers, reported particularly high off-label rates for antidepressants (55.2%) and, especially, for antipsychotics (81.7%) [15], an order of magnitude close to that observed in our series for the second psychotropic medication (77.8%). Comparable rates have also been reported in Greece by Pesiou *et al.,*[16] and, historically, by Zito *et al.,*in their threecountry comparison [17].

Several factors may explain why our prevalence lies at the upper end of this international range. First, the choice of the FDA reference framework, while broader than the European framework for some molecules, remains more restrictive than the actual regulatory context for others, as illustrated by melatonin, which is classified as a dietary supplement by the FDA and

therefore systematically off-label. Second, our study was conducted in a tertiary referral university hospital center, which receives patients with often more severe or complex clinical presentations, for whom recourse to off-label treatment is more frequent than in a first-line outpatient population. Third, the limited availability of certain therapeutic alternatives in Morocco, including the absence of marketed psychostimulants and the limited range of pediatric-appropriate formulations, compels prescribers to use available but not specifically approved molecules for the targeted indication, as illustrated by the case of clonidine in ADHD (see 4.3.3). Finally, differences in recruitment (hospital-based versus outpatient population) may also account for part of the variability observed between our study and international data.

4.3. Prescribing by therapeutic class

4.3.1. Selective serotonin reuptake inhibitors (SSRIs)

Off-label SSRI prescriptions in our series showed marked heterogeneity depending on the molecule: 50% for sertraline, 19.4% for fluoxetine, and none for escitalopram. This variability directly reflects the narrow and specific scope of the pediatric indications approved by the FDA for each molecule. Fluoxetine, the only SSRI with a dual pediatric indication (major depressive episode from age 8, obsessive-compulsive disorder from age 7), logically showed the lowest off-label rate among the SSRIs in our series, despite now-robust evidence in anxiety disorders, as demonstrated by the randomized trial of Birmaher *et al.,*[18]. Sertraline, conversely, is approved by the FDA only for obsessive-compulsive disorder; its predominant use in our series for depressive disorders therefore mechanically constitutes off-label prescribing, even though its efficacy in childhood anxiety disorders is well established by the multicenter CAMS trial of Walkup *et al.,*[19]. This gap between the scientific literature and the regulatory scope is likewise documented by Rosland et al., who report that sertraline remains the most frequently prescribed antidepressant outside its approved indication [7].

4.3.2. Second-generation antipsychotics

Among the antipsychotics prescribed as the first psychotropic medication, risperidone showed the lowest off-label rate (3.7%), whereas quetiapine, aripiprazole, and olanzapine were off-label in all of their prescriptions as the second psychotropic medication. The low off-label rate for risperidone is explained by the breadth of its FDA-approved pediatric indications (adolescent schizophrenia, bipolar I disorder, irritability associated with ASD), which covers a substantial proportion of its common clinical uses. Quetiapine, in contrast, holds no approved pediatric indication other than schizophrenia and bipolar I disorder; its frequent use at low doses for sedative and anxiolytic purposes, a practice already described by Taurines *et al.,*[15] and by Zhaojian *et al.,*[20] in their respective analyses of off-label antipsychotic prescribing, explains the near-systematic shift toward off-label use observed in our series. Although widespread, this practice is explicitly discouraged by professional guidelines: the National Institute for Health and Care Excellence advises against the first-line use of an atypical antipsychotic in nonpsychotic depressive and anxiety disorders in children [3], while the American Academy of Child and Adolescent Psychiatry recommends reserving off-label atypical antipsychotics for situations in which validated treatments have failed, following a rigorous benefit-risk assessment [4].

4.3.3. Clonidine

Clonidine represents the most striking finding of our study regarding individual molecules: 100% of its prescriptions, all issued for ADHD, were off-label. This finding is explained primarily by a local accessibility factor rather than by an absence of clinical rationale: although the FDA has approved the extended-release formulation of clonidine for ADHD in children aged 6 to 17 years, only the immediate-release formulation is marketed in Morocco, with no recognized indication for ADHD, aggression, or associated sleep disturbances. This finding contrasts with the most recent international data: Rosland et al., conversely, report that ADHD treatments show the lowest off-label proportion in their series, owing to the diversification of approved options (methylphenidate, atomoxetine, lisdexamfetamine, guanfacine) [7]. The Moroccan case thus illustrates a situation in which off-label use does not reflect a lack of scientific evidence but rather a constraint in local therapeutic supply: in the absence of marketed psychostimulants in Morocco, clonidine constitutes one of the few available options for patients who do not respond to, or do not tolerate, atomoxetine, the only molecule specifically approved for ADHD in our country.

4.3.4. Melatonin

Melatonin was off-label in 100% of prescriptions in our series, a finding that, as with clonidine, relates more to the regulatory status of the molecule than to a lack of clinical evidence. Under the FDA reference framework used in our study, melatonin is not recognized as a drug but classified as a dietary supplement, rendering any pediatric prescription off-label by definition, including in autism spectrum disorder, where several randomized trials have nonetheless demonstrated a significant efficacy on sleep-onset latency, with a favorable tolerability profile over two years of follow-up [21]. This situation differs from the European framework, where the European Medicines Agency has approved a prolonged-release pediatric formulation for insomnia associated with ASD [6]. Our findings thus illustrate a case in which the definition of off-label use depends almost entirely on the reference framework chosen rather than on the level of available evidence, which warrants a cautious interpretation of this result.

4.4. Prescribing by diagnosis

4.4.1. ADHD

ADHD showed one of the highest off-label proportions among diagnoses in our series (78.9% for the first psychotropic medication), a finding that directly contrasts with that of Rosland *et al.,*in Norway, where ADHD was, conversely, the diagnosis associated with the lowest off-label rate [7]. This discrepancy is explained mainly by the central role of clonidine in our series: the absence of marketed psychostimulants in Morocco directs a substantial proportion of prescriptions toward molecules not approved for this indication, whereas countries with a broader therapeutic arsenal for ADHD are able to limit off-label use for this diagnosis.

4.4.2. Anxiety disorders

Anxiety disorders showed the highest off-label proportion of all diagnoses in our study (100% for the first psychotropic medication). This finding is consistent with international data: according to the FDA, no SSRI holds a primary indication for childhood anxiety disorders other than escitalopram, whereas the clinical practice guidelines of the American Academy of Child and Adolescent Psychiatry place SSRIs, particularly sertraline, at the forefront of recommended pharmacological treatments for this indication, based on solid randomized trial evidence [19,22]. This gap between clinical recommendations and the strict regulatory scope accounts for nearly all of the off-label use observed for this diagnosis, with sertraline and hydroxyzine particularly illustrating this situation.

4.4.3. Depression

Depressive disorder showed an intermediate off-label proportion (17.6% for the first psychotropic medication), lower than that of ADHD or anxiety disorders. This finding is explained by the availability of fluoxetine, the only molecule holding FDA approval for major depressive episodes in children from age 8, which was widely used in our series for this diagnosis. Off-label prescriptions identified for this diagnosis mainly involved sertraline and, as a second-line agent, quetiapine, the latter being used as an adjunctive sedative or anxiolytic agent rather than for a true antidepressant indication, a practice already described by Taurines *et al.,*[15].

4.4.4. Autism spectrum disorder (ASD)

ASD showed a moderate off-label proportion (27.3% for the first psychotropic medication), lower than that of ADHD and anxiety disorders. This lower proportion is explained by the existence of pediatric indications specifically approved by the FDA for risperidone and aripiprazole in the treatment of irritability associated with ASD, two molecules frequently used in our population. Melatonin, although off-label according to the reference framework used, is one of the best scientifically supported treatments for insomnia associated with ASD [21], which again illustrates the disconnect between regulatory status and level of clinical evidence for this diagnosis.

4.4.5. Psychotic disorders

No off-label prescriptions were observed among patients with a psychotic disorder in our series. This finding is explained by the availability, for this indication, of several antipsychotics with broad and well-established pediatric approval (risperidone, aripiprazole, olanzapine for adolescent schizophrenia), which cover nearly all therapeutic needs in this population, in contrast to more peripheral indications (behavioral disorders, insomnia, anxiety) for which the regulatory scope remains considerably narrower.

4.5. Factors associated with off-label prescribing

In our study, off-label status for the first psychotropic medication was significantly associated with age group, primary diagnosis, and prescribed molecule, but not with sex. This latter finding is consistent with most available pharmacoepidemiological studies, which generally do not find a robust association between sex and off-label use [7,9], with differences in prevalence between boys and girls more likely reflecting the distribution of psychiatric diagnoses than sex differentiated prescribing practices.

The significant association between younger age and off-label use (11.7 ± 4.4 years versus 13.9 ± 3.5 years among patients receiving an on-label prescription) is consistent with the findings of several pharmacoepidemiological studies, notably those of Rosland *et al.,* and Carton et al., who report an increased frequency of off-label use among younger children [7,9]. This phenomenon may be explained by several non-exclusive mechanisms: pediatric clinical trials, already few in number, most often include adolescents rather than young children, for methodological and ethical reasons, which further limits approved indications in the youngest age groups; the lower age limits set by marketing authorizations mechanically exclude a proportion of young children who nonetheless require pharmacological treatment; finally, clinical presentations observed in young children may be atypical or may not strictly match the diagnostic criteria used as the basis for registration trials, which favors the use of molecules or dosages not specifically validated for this age group.

4.6. Why is off-label prescribing so frequent?

Beyond the specific analyses by molecule and diagnosis, the high frequency of off-label prescribing observed in our study, as in the international literature, is explained by several structural factors inherent to child and adolescent psychopharmacology. The first relates to the persistent scarcity of randomized clinical trials conducted specifically in children, owing to well-documented methodological and ethical difficulties: the small size of eligible pediatric populations for certain rare or early-onset conditions, legitimate reluctance among families and ethics committees regarding the

inclusion of children in drug trials, a placebo effect that is often pronounced and complicates the statistical demonstration of benefit, and the high cost of these trials relative to the limited commercial market they represent for the pharmaceutical industry [5]. This structural shortfall in pediatric clinical trials has resulted in only a limited number of molecules obtaining a specific pediatric marketing authorization, even though actual clinical needs span a much broader spectrum of conditions, age groups, and clinical situations.

In the face of this insufficient regulated supply, professional society guidelines explicitly acknowledge the need, in certain well-defined clinical situations, to resort to off-label prescribing based on the best available evidence, an individualized benefit-risk assessment, and enhanced clinical monitoring [4,10,23]. Off-label use should therefore not be interpreted as an indicator of poor practice: in the large majority of situations observed in our study, it reflects a necessary clinical adaptation to a still-incomplete regulatory framework rather than an inappropriate or scientifically unfounded use, as evidenced by the fact that nearly all identified off-label prescriptions concerned the indication criterion rather than age or dose.

4.7. Clinical implications

These findings call for several practical implications for clinicians and healthcare institutions. At the individual level, better informing families about the off-label nature of certain prescriptions, their clinical justification, and the available level of evidence appears essential, within a shared decision-making approach. Enhanced clinical and paraclinical monitoring, tailored to the tolerability profile of each molecule (metabolic monitoring for atypical antipsychotics, cardiovascular monitoring for clonidine), should systematically accompany these prescriptions. At the institutional level, the development of local off-label prescribing protocols, collegially validated within child and adolescent psychiatry departments, would help harmonize practices and further secure these prescriptions. Finally, strengthening pharmacovigilance systems dedicated to the pediatric population and developing Moroccan national guidelines that take into account local specificities in therapeutic availability would constitute important levers for regulating this unavoidable but currently under-formalized practice in our context.

4.8. Strengths of the study

This study has several strengths worth highlighting. To our knowledge, it is one of the first studies of this kind conducted in this university hospital center, providing original data on an issue that has so far been poorly documented in the Moroccan context. The explicit and transparent choice of the FDA reference framework for defining off-label status provides our results with a clear and reproducible methodological basis, facilitating comparison with international studies using the same framework. The joint analysis at both the patient and prescription levels, together with the comparison between the first and second prescribed psychotropic medications, allows for a more nuanced understanding of the phenomenon than a strictly global approach. The statistical analyses performed were comprehensive and systematic across all available clinical variables. Finally, this study reflects a real-world clinical population, drawn from the routine practice of a university hospital child and adolescent psychiatry department, which strengthens the direct clinical relevance of its findings.

4.9. Limitations

This study also has several limitations that should be noted for a cautious interpretation of the results. It is a retrospective, single-center study conducted within a single child and adolescent psychiatry department over a short period, which exposes it to potential recruitment bias and does not guarantee the representativeness of the sample relative to other Moroccan institutions. The sample size, although sufficient for the overall descriptive analysis (n = 112), remains limited for subgroup analyses, particularly regarding the second prescribed psychotropic medication (n = 36), which restricts the statistical power of these analyses and requires that certain results be considered indicative rather than confirmatory. No multivariable analysis was performed, which precludes adjustment of the observed associations for potential confounding factors or the identification of independent determinants of off-label status. The exclusive use of the FDA reference framework constitutes another important limitation: as approved pediatric indications vary substantially between the FDA, the European Medicines Agency, and the Moroccan regulatory framework, the prevalence reported in this study is closely dependent on the chosen reference framework and cannot be directly extrapolated to an estimate based on another framework. Finally, this study did not have data on exact dosage, treatment duration, adherence, or clinical outcomes, which precludes an assessment of the actual benefit-risk ratio of the identified off-label prescriptions or a judgment of their individual clinical justification.

4.10. Conclusion

Our study shows that a substantial proportion of patients followed in child and adolescent psychiatry in Morocco receive at least one off-label psychotropic prescription, with a particularly high frequency for the second introduced psychotropic medication. Off-label use mainly concerns a small number of well-identified molecules and diagnoses — clonidine in ADHD, melatonin and quetiapine as combination therapy, anxiety disorders — reflecting regulatory and therapeutic accessibility constraints more than inappropriate clinical use. These findings, consistent with international data while revealing specificities of the Moroccan context, highlight the need for enhanced clinical oversight of this practice. Larger, prospective, multicenter studies are

needed to confirm these trends and inform the development of appropriate national guidelines.

REFERENCES

1. World Health Organization. Mental health of adolescents. Geneva: World Health Organization; 2024. Available from: https://www.who.int/news-room/factsheets/detail/adolescent-mental-health
2. Solmi M, Radua J, Olivola M, Croce E, Soardo L, de Pablo GS, *et al.,*Age at onset of mental disorders worldwide: large-scale meta-analysis of 192 epidemiological studies. Mol Psychiatry. 2022; 27:281–295. doi:10.1038/s41380-021-01161-7.
3. National Institute for Health and Care Excellence (NICE). Depression in children and young people: identification and management. NICE Guideline NG134. London: NICE; 2019. Updated 2024.
4. McClellan J, Stock S; American Academy of Child and Adolescent Psychiatry (AACAP) Committee on Quality Issues. Practice Parameter for the Use of Atypical Antipsychotic Medications in Children and Adolescents. J Am Acad Child Adolesc Psychiatry. 2011;50(9):976–990.
5. Frattarelli DAC, Galinkin JL, Green TP, Johnson TD, Neville KA, Paul IM, Van Den Anker JN; American Academy of Pediatrics Committee on Drugs. Off-label use of drugs in children. Pediatrics. 2014;133(3):563–567. doi:10.1542/peds.2013-4060.
6. European Medicines Agency. Paediatric medicines: overview [Internet]. Amsterdam: European Medicines Agency; [cited 2026 Jul 22]. Available from: https://www.ema.europa.eu/en/human-regulatory-overview/paediatric-medicinesoverview
7. Rosland HG, Engeland A, Furu K, Karlstad Ø, Handal M. Off-label prescribing of psychotropic drugs to children and adolescents in Norway: a nationwide drug utilization study. BMC Psychiatry. 2025; 25:544. doi:10.1186/s12888-025-07058-z.
8. Steinhausen HC. Recent international trends in psychotropic medication prescriptions for children and adolescents. Eur Child Adolesc Psychiatry. 2015;24(6):635–640. doi:10.1007/s00787-014-0631-2.
9. Carton L, Cottencin O, Lapeyre-Mestre M, *et al.,*Off-label prescribing of psychotropic drugs in children and adolescents: a systematic review. Expert Opin Drug Saf. 2015;14(10):1583–1599. doi:10.1517/14740338.2015.1088827.
10. Gazarian M, Kelly M, McPhee JR, Graudins LV, Ward RL, Campbell TJ. Off-label use of medicines: consensus recommendations for evaluating appropriateness. Med J Aust. 2006;185(10):544–548. doi:10.5694/j.1326-5377. 2006.tb00727. x.
11. U.S. Food and Drug Administration. Understanding Unapproved Use of Approved Drugs
12. ("Off-Label") [Internet]. Silver Spring (MD): U.S. Food and Drug Administration; [cited 2026 Jul 22]. Available from: https://www.fda.gov/drugs/information-consumers-andpatients-drugs/understanding-unapproved-use-approved-drugs-label
13. European Medicines Agency. Off-label use [Internet]. Amsterdam: European Medicines Agency; [cited 2026 Jul 22]. Available from: https://www.ema.europa.eu/en/glossary/offlabel-use
14. Neubert A, Wong ICK, Bonifazi A, Catapano M, Felisi M, Baiardi P, Giaquinto C, Knibbe CAJ, Sturkenboom MCJM, Ghaleb MA, Ceci A. Defining off-label and unlicensed use of medicines for children: results of a Delphi survey. Pharmacol Res. 2008;58(5-6):316–322. doi: 10.1016/j.phrs.2008.09.007.
15. Samouh Y, Meftah A, Rahmoune I, Benjelloun G, Filali H. Étude transversale de prescription hors-AMM des psychotropes chez l'enfant et l'adolescent [Cross-sectional study of off-label psychotropic prescribing in children and adolescents; article in French]. Neuropsychiatr Enfance Adolesc. 2021;69(8):422–426. doi: 10.1016/j.neurenf.2021.03.003.
16. Taurines R, Gerlach M, Correll CU, Plener PL, Malzahn U, Egberts KM, *et al.,*Off-label drug use in children and adolescents treated with antidepressants and antipsychotics: results from a prospective multicenter trial. Child Adolesc Psychiatry Ment Health. 2025; 19:1.
17. Pesiou S, Barcelo R, Papazisis G, Torres F, Pontes C. Prevalence of use of on-label and off-label psychotropics in the Greek pediatric population. Front Pharmacol. 2024; 15:1348887.
18. Zito JM, Safer DJ, de Jong-van den Berg LTW, Janhsen K, Fegert JM, Gardner JF, *et al.,*A three-country comparison of psychotropic medication prevalence in youth. Child Adolesc Psychiatry Ment Health. 2008; 2:26.
19. Birmaher B, Axelson DA, Monk K, Kalas C, Clark DB, Ehmann M, *et al.,*Fluoxetine for the treatment of childhood anxiety disorders. J Am Acad Child Adolesc Psychiatry. 2003;42(4):415–423.
20. Walkup JT, Albano AM, Piacentini J, *et al.,*Cognitive Behavioral Therapy, Sertraline, or a Combination in Childhood Anxiety. N Engl J Med. 2008; 359:2753–2766.
21. Zhaojian W, Meizhu J, Jun H, Shanshan G, Jiping H, Zhigang Z, Ying G, Cao L. Trends and off-label utilization of antipsychotics in children and adolescents from 2016 to 2021 in China: a real-world study. Child Adolesc Psychiatry Ment Health. 2024;18(1):77. doi:10.1186/s13034-024-00766-4.
22. Gringras P, Nir T, Breddy J, Frydman-Marom A, Findling RL. Efficacy and safety of pediatric prolonged-release melatonin for insomnia in children with autism spectrum disorder. J Am Acad Child Adolesc Psychiatry. 2017;56(11):948–957.
23. Walter HJ, Bukstein OG, Abright AR, *et al.,*Clinical Practice Guideline for the Assessment and Treatment of Children and Adolescents with

Anxiety Disorders. J Am Acad Child Adolesc Psychiatry. 2020;59(10):1107–1124.
24. Canadian ADHD Resource Alliance (CADDRA). Canadian ADHD Practice Guidelines. 4th ed. Toronto (ON): CADDRA; 2018.

Supplementary Material

The table below provides additional detail on the factors associated with off-label status for the second prescribed psychotropic medication (analysis performed on a restricted subsample, n = 36; results should be interpreted with caution given the low statistical power).

Supplementary Table S1. Factors associated with off-label status of the second prescribed psychotropic medication (n = 36).

Variable	Off-label n (%)	On-label n (%)	p
Sex Female	13 (76.5%)	4 (23.5%)	1.000
Male	15 (78.9%)	4 (21.1%)	
Age group 6-11 years	2 (100%)	0 (0.0%)	1.000
12-18 years	26 (76.5%)	8 (23.5%)	
Primary diagnosis Psychotic disorder	2 (100%)	0 (0.0%)	0.137
Depressive disorder	14 (87.5%)	2 (12.5%)	
ADHD	1 (33.3%)	2 (66.7%)	
OCD	4 (100%)	0 (0.0%)	
ASD	4 (66.7%)	2 (33.3%)	
Molecule Aripiprazole	2 (100%)	0 (0.0%)	**0.0001**
Fluoxetine	0 (0.0%)	2 (100%)	
Hydroxyzine	0 (0.0%)	5 (100%)	
Melatonin	12 (100%)	0 (0.0%)	
Quetiapine	8 (100%)	0 (0.0%)	
Risperidone	3 (75.0%)	1 (25.0%)	

Fisher's exact test used for 2 × 2 comparisons with low expected cell counts. The bold p-value indicates a statistically significant association (threshold 0.05).