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Unlicensed and off-label use of psychotropic medications in French children: a prospective study

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The number of medicinal products currently labelled for paediatric use is limited. Prospective studies have provided useful information in relation to the extent of use of unlicensed and off label medicines in children. As the use of psychotropic agents in children has increased in the recent years, the present study was undertaken to analyse their use in a Department of Child and Adolescent Psychiatry and identify priorities for research.

Three hundred and thirty six hospitalised children were included and 295 prescriptions were analysed prospectively. For each patient, age, diagnosis and treatment were recorded and all prescriptions were assessed for unlicensed and off label use. 48% of prescriptions were either unlicensed or off label. The three main groups of drugs prescribed were antipsychotics, stimulants and antidepressants. The level of unlicensed and off label drug use within each group was as follows: antidepressants (80%), antipsychotics (46%) and stimulants (10%). Three drugs (cyamemazine, methylphenidate and risperidone) accounted for more than 50% of all prescriptions. According to our results, priorities for research should primarily focus on antidepressants to make safe and effective medicines available for children with depression.

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Introduction

Many children often receive drugs that are either unlicensed or used off label but the extent of such prescriptions varies according to the type of drug, the diagnosis and age of the patient. Numerous studies have been conducted in paediatric wards[1-3], ambulatory units[4] and in general practice[5, 6] to quantify this problem. In general practice, 29% of prescriptions were off label and 4% unlicensed. Data were obtained in different countries in Europe[1, 7-9], North America, Australia[10] and Israel[4].

As the use of psychotropic agents in children has increased in recent years[11-13], the aim of the present study was to look at off label and unlicensed use of psychotropic agents in a Child and Adolescent Psychiatry Department.

Methods

Psychotropic drugs are defined as those that affect mood and behaviour. Five classes were initially suggested by the World Health Organisation in 1967: antipsychotic drugs, anxiolytic sedatives, antidepressant drugs, psychomotor stimulants (and hallucinogenic drugs) (Table 1). In addition, normothymics are more recent psychotropic medicines, primarily used in affective disorders characterised by changes in mood (depression or mania) defined as bipolar disorders. The reference drug in adults is lithium and additional drugs in this group are valproate derivates. This prospective study was conducted between January and June 2002. Data were prospectively collected on all paediatric inpatients in the Child and Adolescent Psychiatry Department. Patients' age, sex, weight, duration of hospitalisation and diagnosis (according to the Diagnostic and Statistical Manual for Mental Disorders DSM version IV) were recorded.

When a psychotropic medication was prescribed, the following items were noted: trade and scientific names, dose, frequency, route of administration, formulation (tablets, syrup, drops) and duration of treatment. All drugs administered were assessed for unlicensed and off label use, according to a classification system already described[14]. Unlicensed drugs do not have a product licence or marketing authorisation. A few drugs, licensed for adult use, are not recommended in children and were identified as "unlicensed for use in children". Off label corresponds to use outside the terms of the product license, included in the national French compendium (Vidal 2002, Table 1). Use of a medicine may be off label for several reasons: dose (administration of doses higher or lower than recommended), age (patients outside the age range for which the drug is licensed), indication (indication not covered by the licence), formulation, route, contraindication.

Data analysis

The database, containing anonymous data was constructed using the EpiInfo software (version 6.04.fr, Atlanta 2000). Statistical analysis was by SAS (The SAS System for Windows version 8.2). Chi-squared analysis was carried out for categorical data, Student's *t*-test for group comparisons of continuous parametric data and Mann-Whitney *U*-test or Fischer exact test for group comparisons of ordinal (non-parametric) data with a P value < 0.05.

Results

Three hundred and thirty six children aged 3 to 15 years were analysed and 162 (48.2%) children received one or more psychotropic medications while 174 (51.8 %) did not receive any medicine (Table 2). The treated patients were older than the untreated patients ($P<0.05$, Table 2). The sex ratio

Table 1 Licensing status of psychotropic medications prescribed

Therapeutic class	Drug	Licensing status for children in France (years)
Antipsychotics (neuroleptics)		
Phenothiazines	Alimemazine	Children ≥1*
	Chlorpromazine	Children ≥ 3*
	Cyamemazine	Children ≥ 6*
	Levomepromazine	Children ≥ 3*
	Propericiazine	Children ≥ 3*
Butyrophenomes	Haloperidol	Children ≥ 3*
Benzamides	Amisulpride	Contraindicated < 15*
	Tiapride	Children ≥ 6*
Dibenzodiazepines	Clozapine	NI
	Olanzapine	NR
Others	Loxapine	Contraindicated < 16*
	Risperidone	NR*
Anxiolytics		
Benzodiazepines	Alprazolam	Children ≥ 6
	Clonazepam	All ages*
	Chlorazepate	Children ≥ 6
	Diazepam	All ages*
	Lorazepam	Children ≥ 6
Hydroxyzine	Hydroxyzine	Children ≥ 30 months
Antidepressants		
SSRIs	Venlafaxine	Contraindicated < 18
	Citalopram	Contraindicated < 15*
	Fluoxetine	Contraindicated < 15*
	Paroxetine	Contraindicated < 15*
	Sertraline	Children ≥ 6
	Mianserine	Contraindicated < 15
Others	Mirtazapine	NR
Stimulants		
	Modafinil	NI
	Methylphenidate	Children ≥ 6
Normothymics		
Valproate derivates	Valproic acid	All ages
	Valpromide	NI
	Sodium divalproate	NR <18
Others		
Opioid antagonists	Naltrexone	NI
	Tropatepine	NI

*liquid formulation available; NR not recommended for children; NI No information in children

Table 2 Age and diagnosis of patients

	Treated patients	Untreated patients
Number of patients	162	174
Age		
2-5 years (%)	14 (9)	49 (28)
6-11 years (%)	79 (49)	98 (56)
12-15 years (%)	69 (42)	27 (16)
Major diagnosis (*n*)		
ADHD	67	17
Depressive disorder	26	0
Eating disorders	11	12
Anxious disorders	10	10
Bipolar disorders	9	1
Schizophrenia (psychotic disorders)	7	0
Developmental delay	7	41
Pervasive developmental disorders	7	17
Tourette disorders	6	3
Communication disorders	1	22
Others	11	52

was similar in the two groups (30 % females) but the girls were older than the boys at the initiation of treatment. In addition, diagnosis was different between the treated and untreated groups. Most of the patients presenting with Attention Deficit Hyperactivity Disorder (ADHD *n*=84), depression (*n*=26), schizophrenia and psychotic disorders (*n*=17) were treated while only a limited number of patients with developmental delay, a communication disorder or an eating disorder received a psychotropic medication.

Two hundred and ninety five prescriptions corresponding to 33 different psychotropic medications were analysed. Between one and six drugs were administered per patient (mean = 2) with a majority of children (*n* = 83, 51 %) receiving only one medication. 48% of the prescriptions were off label or unlicensed (Table 3). The predominant therapeutic classes included antipsychotics, stimulants and antidepressants. In all cases, the drugs prescribed had a marketing authorisation but for nine drugs (67 prescriptions, 23%) there was either no information on children or the drug was not recommended for use in children. Sixteen drugs were used off label in 75 (25%) prescriptions. Eight drugs were contraindicated in children and prescriptions were off label for age, dosage, formulation or indication for the other eight drugs (Table 4). Three drugs (cyamemazine, methylphenidate and risperidone) accounted for more than 50 % of all prescriptions and five (fluoxetine and sodium divalproate in addition) accounted for more than 70 % of all prescriptions.

The psycho-stimulant, methylphenidate, was administered to 67 children: 65 with ADHD (two ADHD young patients received another drug) and two patients with Tourette disorder. As methylphenidate is licensed for ADHD in children over the age of 6 and is available as tablets, prescription was off label for age and formulation in 6 patients younger than 6 years.

Risperidone, an atypical antipsychotic, was administered to 34 patients: 10 presenting with ADHD, six with Tourette disorder and 18 with other symptoms. It was used off label in all cases. Methylphenidate and risperidone were given in combination in 12 patients; 10 with ADHD and two with Tourette disorder.

Antidepressants were administered to 61 patients. Fluoxetine was used for 11 children with depression and for nine patients with obsessive compulsive disorder (OCD). All antidepressants were used off label as sertraline (15 prescriptions) is labelled for use in children over 6 but only with the indication of OCD.

Cyamemazine is a neuroleptic phenothiazine that was prescribed in 71 patients to treat clinical symptoms of agitation and aggressiveness complicating psychiatric disorders such as communication and pervasive developmental disorders. Cyamemazine was used off label in 12% cases, as the intramuscular route of administration was used although not recommended in children.

Table 3 Prescriptions of psychotropic drugs

	Number of prescriptions	Number of off label or unlicensed prescriptions	% off label and unlicensed
Antipsychotics	137	63	46
Stimulants	68	7	10
Antidepressants	61	49	80
Normothymics	17	17	100
Anxiolytics	9	4	44
Others	3	2	67
Total	295	142	48

Discussion

In the present prospective study 48% of prescriptions for psychotropic drugs were either unlicensed or off label. It is recognised that many drugs used in children are either unlicensed or off label, both in office based practice[6] and in hospitalised children[10]. The numerous reasons for using unlicensed and off label drugs in children have been extensively discussed in recent years and the rational use of medicines in children is being addressed in both American and European initiatives[14-16].

In paediatrics, the use of unlicensed and off label psychotropic medications is of special concern. Drugs of this therapeutic class are needed in paediatrics. Similarly to adults, children may develop psychiatric disorders because of familial and/or environmental stresses and they may even be more susceptible than adults to these different stresses. The prevalence of major depression is 3% in children and adolescents and OCD occurs in 1–3% of children. In addition, the prevalence of

Table 4 Off label and unlicensed drug prescriptions

Category	Number of prescriptions	%
Off label		
Indication	9	
Age	6	
Dosage	2	
Formulation	20	
Subtotal*	31	11
Contra indicated	44	15
Total off label prescriptions	**75**	**25**
Unlicensed		
No information on use in children	5	
Not recommended in children	62	
Total unlicensed prescriptions	**67**	**23**

*One drug prescription can be classified as off label for more than one reason

psychiatric disorders is probably underestimated, as they may be difficult to diagnose, particularly in young children. Psychiatric disorders may be different in children and adults and options for drug treatment should be evaluated. Although serious deleterious consequences may be associated with no treatment, psychotropic drugs may have an impact on neurological and behavioural development and should be considered high risk prescriptions.

Data on off label use of antipsychotic drugs are very limited. According to a recent survey, 66% of adult patients treated with an antipsychotic were receiving the drug for off label indications[17]. In children, while the evaluation of psychotropic drugs is limited, off label use is expanding rather than decreasing, as reported in numerous countries both in Europe and the USA[11, 18]. In most studies, stimulants were the most commonly prescribed drugs, but antidepressants, anxiolytics, antipsychotics and mood stabilisers were also prescribed[11, 13, 19].

In our study, the decision to initiate a psychotropic treatment was clearly dependent upon the underlying illness, as most children admitted with ADHD, depression and schizophrenia were treated while only a limited number of patients with developmental delay, a communication disorder or an eating disorder received a psychotropic medication. In addition, the younger patients received medicines less frequently than the older patients.

The predominant therapeutic classes include antipsychotics and antidepressants, accounting for 67% of prescriptions. Stimulants were prescribed in children with ADHD. ADHD is considered as a common behavioural disorder among school-age children, affecting approximately 5 – 10% of them although not always requiring treatment[20]. Stimulants have been shown to be effective, improving the score symptoms of this disease and are recommended as first line therapy in patients with ADHD[21-23], although controversies persist about the risks of over-diagnosis and over-prescription[24]. In addition, ADHD is frequently associated with other neurobehavioural disorders resulting in co-administration of stimulants with tricyclic antidepressants or alpha agonists without evaluation of efficacy and safety[25-28]. Methylphenidate has a short elimination half-life and should be taken twice daily. The slow release form, given once daily, is waiting for a marketing authorisation in France and will improve the management of affected children.

Risperidone, a new generation antipsychotic medication prescribed for the treatment of several neuropsychiatric developmental disorders, was administered off label in patients having ADHD and Tourette disorder. However, the efficacy and safety of risperidone has been evaluated in children with mild developmental delay by pilot short-term double-blind placebo-controlled trials and was more effective than placebo in reducing conduct disorders and aggressive behaviours[29-32]. The drug was also effective for the short-term treatment of patients with Tourette syndrome and related disorders, although the data remain limited and the drug used off label[33-35].

Major depression is thought to occur in 0.5% of pre-school and 2% of school-age children[36]. Tricyclic antidepressants, which were used for the treatment of depression in adults, are known to have limited efficacy and reduced safety compared to the newer antidepressants in children and primarily to selective serotonin reuptake inhibitors (SSRIs)[37]. This explains why clinicians, both specialists and general practitioners[38] prescribe SSRIs in children although little is known about the efficacy and safety in paediatric patients. In the present study, children hospitalised for depression received a selective serotonin reuptake inhibitor (SSRI) as a first choice drug. Fluoxetine was the first licensed drug for adult use in this class. In children, two double-blind studies[39, 40] gave rise to discordant results : the study by Simeon[39] failed to show efficacy while the study by Emsli[40] that included 96 children with depression, demonstrated that fluoxetine was superior to placebo in reducing symptoms of depression. The other SSRIs, although prescribed in children, have limited pharmacokinetics and clinical evaluation in children. Some data are available with paroxetine[41, 42], sertraline[43, 44], fluvoxamine[45] and venlafaxine[46]. However, recent data suggested that SSRIs may increase the risk of suicidal thoughts, behaviour disturbances and self harm in young people. The Committee on Safety of Medicines in the United Kingdom has advised against use of most of the antidepressant drugs in the selective serotonin uptake inhibitor group for major depressive disorder in children and adolescents under the age of 18 years[47, 48].

Conclusion

Approximately half the prescriptions for psychotropic medicines in a specialised psychiatric ward treating children are off label or unlicensed. An early evaluation of these drugs should be undertaken. In particular, additional clinical trials should be performed to evaluate the safety and efficacy of antidepressants including SSRIs in children and establish guidelines for the treatment of depressive children and adolescents.

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