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ORIGINAL REPORT

Psychiatric adverse drug reactions reported during a 10-year period in the Swedish pediatric population

Maria Bygdell, Gertrud Brunlöf, Susanna M. Wallerstedt and Jenny M. Kindblom*

Clinical Pharmacology, Institute of Medicine, the Sahlgrenska Academy at Gothenburg University, Gothenburg, Sweden

ABSTRACT

Purpose Psychiatric Adverse Drug Reactions (ADRs) are frequent in the pediatric population. The aim of the present study was to analyze spontaneously reported psychiatric ADRs in children during a 10-year period.

Methods All spontaneously reported Individual Case Safety Reports (ICSRs) concerning children (<18 years old) and psychiatric adverse reactions assessed as at least possible, registered in the Swedish Drug Information System (SWEDIS) during the period 2001–2010, were extracted and characterized. Age and sex distribution and labeling/registration status were studied.

Results A total of 600 ICSRs concerning 744 psychiatric adverse reactions were identified and included in the analysis. Boys were overrepresented among included ICSRs (60.3% vs. 39.7%; $p < .001$). After exclusion of vaccines, the three most frequently suspected drugs were montelukast, centrally working sympathomimetic drugs, and inhaled glucocorticoids. Serious adverse reactions were reported more frequently for drugs used off-label than for drugs used according to the *Swedish Physician's Desk Reference*. Aggressiveness was reported more frequently for boys than for girls as were suicidal conditions.

Conclusions Psychiatric ADRs in the pediatric population have been reported for a wide range of reactions and drugs and display age and sex differences including a higher number of suicidal reactions in boys. An association was seen between serious reactions and off-label drug use. Further studies are needed to elucidate safety aspects of unlicensed drugs and drugs used off-label and whether there are differences in children's susceptibility to develop ADRs. Copyright © 2011 John Wiley & Sons, Ltd.

KEY WORDS—adverse drug reactions; psychiatric; children; pediatric; off-label; SWEDIS

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INTRODUCTION

Adverse Drug Reactions (ADRs) in the pediatric population are common and have consequences such as patient suffering, hospital admissions, and public health costs.[1–5] Increased knowledge of drug safety is warranted as it would enable a better risk–benefit analysis for patients in the pediatric population. For registered drugs, knowledge from clinical trials is available, although uncommon ADRs cannot be expected to be detected. Furthermore, many registered drugs lack documentation on effects and safety in children but are despite this frequently used in pediatric patients in an off-label manner.[6–8] Drugs used off-label have been suggested to carry an increased risk for ADRs.[9–12] One example of off-label drug use is the use of oral contraceptives commonly prescribed to girls <18 years. Although the effect of oral contraceptives is well documented and thought to reduce teenage abortions,[13,14] safety aspects are not as well understood, and as a consequence, it was not until recently that the negative effects of depot-medroxyprogesterone on bone mass especially in the young who had not yet reached peak bone mass, were discovered.[15] Thus, despite that the use of oral contraceptives in teenaged girls is well established, safety issues caused by lack of documentation in this specific age group were discovered only recently.

Psychiatric adverse reactions are frequent in the pediatric population[3,16,17] and include for example severe reactions such as suicidality, which has been associated with isotretinoin and Selective Serotonin Reuptake Inhibitors (SSRIs),[18–20] as well as less severe reactions such as sleep disorder, anxiety, aggressiveness, and hyperactivity, which have been associated with montelukast and budesonide.[21,22] To the best of our knowledge,

*Correspondence to: J. M Kindblom, Vita Straket 11, SU/Sahlgrenska, S-413 45 Gothenburg, Sweden. E-mail: jenny.kindblom@gu.se

psychiatric ADRs have not been described previously in an overall approach, and therefore, increased knowledge on psychiatric ADRs is needed. To further study and describe ADRs in clinical practice, databases with spontaneously reported ADRs are valuable sources. The Swedish Drug Information System (SWEDIS) is such a database that can be used for detection of safety signals and generation of hypotheses.

The aim of the present study was to characterize the spontaneously reported psychiatric adverse reactions in children during a 10-year period.

METHODS

In the present study, SWEDIS was screened for Individual Case Safety Reports (ICSRs) matching the inclusion criteria (i) registered during the period 2001–2010; (ii) concerning children (<18 years); (iii) concerning the System Organ Class (SOC) *Psychiatric disorder* (codes PS0101-PS9950) according to the preferred term in the Medical Product Agency adverse reaction terminology (MPAart); and (iv) a possible causal relationship between suspected drug(s) and reported ADR. ICSRs concerning infants exposed *in utero* or through breast-feeding were excluded (Figure 1). ICSRs concerning the vaccine Pandemrix were also excluded from the entire study because the association with narcolepsy was under investigation by the Swedish MPA at the time the present study was performed, and all these ICSRs were therefore assessed as unclassified regarding causality. For each ICSR, information was registered on (i) reported individual (sex, age, and recovery); (ii) suspected drug (s) (Anatomic Therapeutic Chemical classification system (ATC)) code level 4 and 6[23]) or if the drug had been used in an unlicensed or off-label manner; and (iii) reaction (classification (according to the MPAart), seriousness, response to withdrawal of the drug (dechallenge), or repeated administration (rechallenge)). An event was defined as a unique combination of a specific drug and a specific reaction in an ICSR. The age groups used were newborns (<1 month), infants (1–23 months), preschool children (2–5 years), children (6–12 years), and adolescents (13–17 years). Analyses of ICSRs and suspected drugs were investigated including vaccines (Table 1 and Figure 1). Further analyses were performed after exclusion of all vaccines (Tables 2, 3 and 4).

In Sweden, physicians, dentists, and nurses are obliged to report (i) serious ADRs; (ii) ADRs not mentioned in the Summary of Product Characteristics (SPC); (iii) ADRs related to the use of new drugs (≤2 years on the market) except those labeled as common in the SPC; and (iv) ADRs that appear to be increasing in incidence, to regional pharmacovigilance centers. The ADRs are registered in SWEDIS, and this ADR database is thus based on spontaneous reporting. In regional pharmacovigilance centers, specially trained nurses and clinical pharmacologists review the ICSRs and assess causality between drug and reaction as well as seriousness of the reaction. According to the World Health Organization Collaborating Centre for International Drug Monitoring, a serious ADR is defined as any untoward medical occurrence

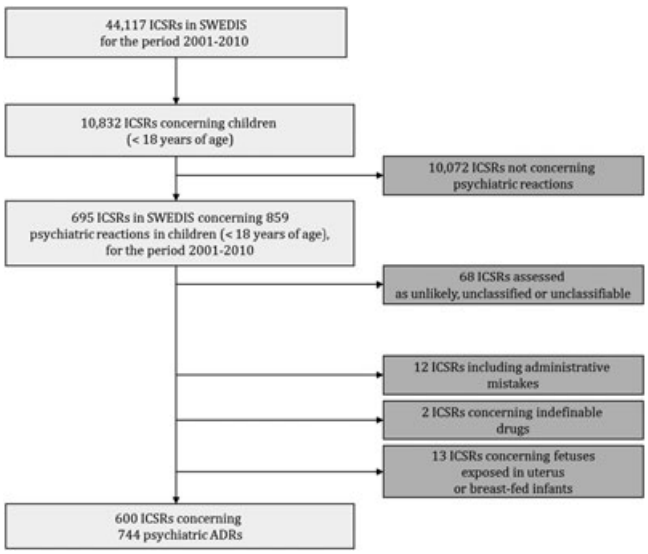

Figure 1. Flow chart of the study design demonstrating data retrieval of spontaneous reports in the Swedish Information System, and inclusion and exclusion criteria in the present study

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Table 1. Drugs suspected in ICSRs concerning psychiatric adverse reactions reported in children

Suspected drug	ATC code	ICSRs *n* (%)	Suspected drugs in ICSRs *n* (%)
Isotretinoin	D10BA01	28 (4.7)	28 (4.3)
Vaccines	J07	278 (46.3)	311 (47.5)
Other antiepileptic	N03AX	10 (1.7)	10 (1.5)
Melatonin	N05CH01	8 (1.3)	8 (1.2)
Selective serotonin reuptake inhibitors	N06AB	19 (3.2)	19 (2.9)
Centrally working sympathomimetic drugs	N06BA	52 (8.7)	54 (8.2)
Adrenergic and other drugs used during obstructive respiratory disorders	R03AK	10 (1.7)	10 (1.5)
Inhaled glucocorticoids	R03BA	39 (6.5)	39 (6.0)
Montelukast	R03DC03	60 (10.0)	60 (9.2)
Combinations of antihistamines	R06AX	10 (1.7)	10 (1.5)
Other		86 (14.3)	106 (16.2)
Total		600 (100)	655 (100)

Drugs or drug groups suspected in <7 ICSRs are included in "other."
ATC, Anatomical Therapeutic Chemical classification, ICSR, Individual Case Safety Report.

that at any dose (i) results in death; (ii) requires inpatient hospitalization or prolongation of existing hospitalization; (iii) results in persistent or significant disability or incapacity; or (iv) is life-threatening.

Assessment of causality between the suspected drug (s) and the ADR(s) is also performed.

Labeling or registration status as well as seriousness of the reaction were assessed by two independent investigators (M.B. and J.M.K.). Off-label and unlicensed drug use was defined according to Neubert *et al*.[24] Off-label use was assessed with respect to age, therapeutic indication, dosage, pharmaceutical form, and route of administration, specified in the *Swedish Physician's Desk Reference* from the year the ICSR was registered (corresponds to the Swedish SPC). Unlicensed drug use was defined as use of drugs without marketing authorization the date the ICSR was registered. ICSRs registered in SWEDIS as serious based on reactions other than the psychiatric ADRs; the psychiatric reaction was classified as nonserious in the present study ($n = 3$). For disagreements, ICSRs were reviewed a second time by the investigators together and consensus reached.

The study was approved by the regional ethical review board in Gothenburg.

Statistical analyses

The extracted ICSRs were collected in a database using the software SPSS 17.0 (SPSS, Chicago, IL). Significance test was performed using Fisher's exact test using the R package statistics (the R foundation for statistic computing, Vienna, Austria; www.r-project.org). For the difference between sexes in reporting, binomial test (SPSS software) was used.

RESULTS

A total of 44 117 ICSRs were registered in SWEDIS during 2001–2010, 600 of which concerned 744 psychiatric adverse reactions in children (Figure 1). A total of 362 (60.3%) ICSRs concerned boys and 238 (39.7%) ICSRs concerned girls ($p < 0.001$). The ICSRs were reported for different age classes: newborns ($n = 3$, 0.5%), infants ($n = 265$, 44.2%), preschool children ($n = 72$, 12.0%), children ($n = 139$, 23.2%), and adolescents ($n = 121$, 20.2%). In 507 (84.5%) ICSRs, the child recovered from the adverse reaction; in 43 (7.2%) ICSRs, the child had not recovered at the time of reporting, and 2 cases (0.3%) were fatal. The number of ICSRs after exclusion of vaccines was 322.

A total of 71 different drug entities (entities counted for chemical subgroup level, i.e., ATC level 4, except vaccines that were counted as one entity) were suspected to have caused the psychiatric adverse reactions. In the present study, 132 events concerned drugs used according to the *Swedish Physician's Desk Reference*. The corresponding figures were 117 for drugs used off-label (7 of which were over-the-counter drugs, drugs used in addiction, drugs taken by mistake, or intoxication) and 42 for unlicensed drugs.

Off-label drug use was more frequently involved in adverse reactions classified as serious when compared with drugs used as labeled (25 ICSRs (21.4%) vs. 10 ICSRs (7.5 %); $p = 0.002$), and off-label according to age was the most common reason for off-label classification (Table 2). The number of ICSRs and reactions per psychiatric MPAart are presented in Table 3. 60 out of 453 (13.2%) psychiatric adverse reactions not related to vaccines were classified as serious. Drugs or drug classes frequently associated with serious psychiatric adverse reactions were SSRIs (ATC code N06AB; 8 ICSRs), isotretinoin (ATC code D10BA01; 7 ICSRs), and centrally working sympathomimetic drugs (ATC code N06BA; 5 ICSRs; Table 3).

For boys, the most frequently reported adverse reactions were aggressiveness, sleep disorder, and affective disorder. For girls, the most frequently reported

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Table 2. Drugs associated with ≥3 cases of off-label drug use and type of off-label use given as number of cases (%)

Suspected drug	ATC code	Drug use contraindicated to the age of the child (A)	Drug use not indicated to the age of the child (B, but not A)	Drug used outside the indications (C, but not A or B)	Drug dose too high (D, but not A, B, or C)	Other administration form or route (but not A, B, C, or D)
Proton pump inhibitors	A02BC	0	3 (2.7)	0	0	0
Gestagens and estrogens	G03AA	0	6 (5.1)	0	0	0
Glucocorticoids	H02AB	0	4 (3.4)	0	0	0
Antiepileptics	N03AX	0	7 (6.0)	1 (0.9)	0	0
Bensodiazepine derivatives	N05CD	0	0	0	1 (0.9)	3 (2.7)
Melatonin	N05CH	0	5 (4.3)	0	0	0
Selective serotonin reuptake inhibitors	N06AB	0	19 (16.2)	0	0	0
Antidepressants	N06AX	0	3 (2.7)	0	0	0
Centrally working sympathomimetics	N06BA	0	1 (0.9)	2 (1.7)	2 (1.7)	0
Inhaled glucocorticoids	R03BA	0	3 (2.7)	0	5 (4.3)	0
Montelukast	R03DC	0	2 (1.7)	2 (1.7)	4 (3.4)	0
Other		3 (2.7)	28 (24.0)	8 (6.8)	4 (3.4)	2 (1.7)
Total		3 (2.7)	81 (69.2)	13 (11.1)	15 (12.8)	5 (4.3)

"Other" includes drugs with ≤2 cases of off-label drug use. If a treatment was off-label in more than one aspect, the off-label drug use was prioritized according to the first off-label (A, B, C, etc.). Off-label prescribing was assessed according to the *Swedish Physician's Desk Reference*, corresponding to the Swedish summary of product characteristics.
ATC, Anatomical Therapeutic Chemical classification, ICSR, Individual Case Safety Report.

adverse reactions were sleep disorder, anxiety, and affective disorder. Aggressiveness was reported more frequently for boys than for girls (52 ICSRs vs. 17 ICSRs, $p = .012$), as were suicidal conditions (12 ICSRs vs. 1 ICSR; $p = .021$). Suicidal conditions (suicide, suicidal attempt, and thoughts of suicide) were reported in 13 ICSRs in total: isotretinoin ($n = 4$), centrally working sympathomimetic drugs ($n = 4$), SSRI ($n = 3$), montelukast ($n = 1$), and antibiotic used for acne ($n = 1$). Twelve of these ICSRs concerned adolescents, and one concerned a child (9 years old; Table 4).

The types of reported psychiatric reactions varied between the age groups (Table 4). Sleep disorder was the most common ADR reported for infants and preschool children: 10 and 18 ICSRs, respectively (40.0% of all ICSRs for infants and 30.5% of all ICSRs for preschool children); aggressiveness for children: 37 ICSRs (30.8% of all ICSRs for children); and for adolescents, affective disorder was the most reported ADR: 32 ICSRs (27.4% of all ICSRs for adolescents).

The four most frequently reported events of a drug or drug class and a psychiatric ADR were montelukast and sleep disorder ($n = 34$), centrally working sympathomimetic drugs and aggressiveness ($n = 17$), isotretinoin and affective disorder ($n = 16$), and inhaled glucocorticoids and aggressiveness ($n = 16$; Table 3).

DISCUSSION

In the present study, we demonstrate that psychiatric ADRs concerning children registered in SWEDIS display age and sex differences. The reports more often concern boys than girls, and the differences were most prominent for the reactions suicidality and aggressiveness. The most frequently reported reaction was aggressiveness for boys and sleep disorder and anxiety for girls. Moreover, the reports in the present study often include unlicensed drugs and drugs used off-label.

ADRs represent an important drug-related problem in children as well as in adults. In a systematic review, the incidence of ADRs in the pediatric population ranged from 4.4% to 16.8%,[1] and in a Danish study, psychiatric reactions were the fourth most commonly reported SOCs, after general disorders, skin and subcutaneous disorders, and nervous system disorders.[17] Furthermore, we recently reported that psychiatric ADRs constitute a major part (24% of the events) of the ADRs reported for children, which was twice as much as that in adults.[25] Thus, psychiatric adverse reactions are some of the most frequently reported ADRs in children, and they are reported for a wide variety of drugs with psychiatric as well as somatic indications.[22,25–28] Despite this, they have not been fully described.[3] To characterize psychiatric ADRs

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Table 3. Reported psychiatric adverse drug reactions in children and association between frequently reported drugs or drug groups (vaccines excluded)

	ICSRs	Reactions		Reactions associated with frequently reported drugs/drug groups (number of ADRs classified as serious, number with positive dechallenge, number with positive rechallenge)				
Psychiatric reaction according to MPAart	n (%)	Total n (%)	Serious n (%)	Isotretinoin (D10BA01)	Selective serotonin reuptake inhibitors (N06AB)	Centrally working sympathomimetic drugs (N06BA)	Inhaled glucocorticoids (R03BA)	Montelukast (R03DC03)
Sleep disorder	76 (17.3)	84 (18.5)	2 (3.3)					
sleep disorder		38	1	1 (1, 0, 0)	3 (0, 1, 0)	4 (0, 2, 1)	7 (0, 7, 3)	11 (0, 10, 2)
insomnia		7	-	0	0	0	0	4 (0, 3, 3)
sleep walking		2	-	0	0	1 (0, 0, 0)	0	0
nightmares		37	1	1 (0, 1, 0)	3 (0, 3, 0)	2 (0, 0, 0)	1 (0, 0, 0)	19 (1, 18, 9)
Aggressiveness	69 (15.7)	69 (15.2)	5 (8.3)	3 (0, 3, 1)	5 (2, 5, 0)	17 (1, 13, 3)	16 (0, 16, 6)	13 (1, 12, 4)
Affective disorder	61 (13.9)	61 (13.5)	6 (10.0)					
depressed mood		35	-	10 (0, 6, 1)	0	5 (0, 4, 0)	5 (0, 4, 3)	5 (0, 5, 0)
depression		23	5	6 (3, 1, 0)	0	6 (1, 3, 0)	3 (0, 3, 1)	1 (0, 1, 1)
hypomania		1	-	0	1 (0, 1, 0)	0	0	0
mania		2	1	0	1 (1, 0, 0)	1 (0, 0, 0)	0	0
Anxiety	44 (10.0)	48 (10.6)	4 (6.7)	6 (1, 3, 2)	2 (1, 2, 0)	6 (1, 3, 0)	8 (0, 8, 0)	9 (0, 9, 1)
Hallucination	41 (9.3)	41 (9.1)	16 (26.7)	0	3 (3, 2, 0)	5 (1, 4, 2)	1 (0, 0, 0)	2 (0, 2, 0)
Personality disorder	38 (8.6)	38 (8.4)	1 (1.7)					
personality disorder		27	1	0	0	7 (0, 4, 0)	4 (0, 4, 1)	9 (0, 8, 5)
apathy		3	-	0	0	1 (0, 1, 0)	1 (0, 1, 1)	1 (0, 1, 0)
emotional lability		6	-	1 (0, 1, 0)	0	2 (0, 1, 0)	1 (0, 1, 0)	0
emotional instability		1	-	0	0	0	0	0
euphoria		1	-	0	0	1 (0, 0, 0)	0	0
Agitation	27 (6.1)	27 (6.0)	2 (3.3)					
agitation		7	1	0	2 (1, 2, 0)	0	1 (0, 1, 0)	0
hyperactivity		18	1	0	0	2 (0, 2, 0)	8 (0, 8, 2)	8 (1, 7, 4)
excitement excessive		2	-	0	1 (0, 1, 0)	1 (0, 1, 0)	0	0
Irritability	17 (3.9)	17 (3.8)	2 (3.3)	1 (0, 1, 0)	0	2 (0, 2, 0)	6 (0, 6, 4)	2 (0, 2, 0)
Suicidal conditions	13 (3.0)	13 (2.9)	10 (16.7)					
thoughts of suicide		7	4	2 (1, 1, 0)	1 (1, 1, 0)	2 (1, 2, 1)	0	1 (1, 1, 0)
suicide attempt		5	5	2 (2, 0, 0)	2 (2, 0, 0)	1 (1, 0, 0)	0	0
suicide		1	1	0	0	1 (1, 0, 0)	0	0
Confusion	11 (2.5)	11 (2.4)	4 (6.7)	0	1 (0, 0, 0)	0	0	0
Concentration impaired	11 (2.5)	11 (2.4)	1 (1.7)	3 (1, 2, 0)	0	0	0	3 (0, 3, 2)
Other	33 (7.5)	33 (7.3)	7 (11.6)	2 (0, 1, 0)	4 (2, 3, 0)	7 (0, 5, 0)	2 (1, 2, 1)	4 (0, 4, 4)
Total	440 (100)	453 (100)	60 (100)	38 (9, 20, 4)	29 (13, 21, 0)	74 (7, 47, 7)	64 (1, 61, 22)	92 (4, 86, 35)

One ICSR may contain more than one reaction. Therefore, the total number of ICSRs derived from adding the number of ICSRs for each adverse reaction group exceeds the total number of ICSRs in the study.
0 denotes negative serious, dechallenge and rechallenge, or lacking information.
ICSR, Individual Case Safety Reports, MPAart, Medical Product Agency adverse reaction terminology.

in children, we conducted a descriptive study on psychiatric ADRs in children in Sweden during a 10-year period based on ICSRs (n = 600) extracted from SWEDIS.

In the present study, we found that more ICSRs were reported for boys than for girls, and this finding is in accordance with results from the Danish study by Aagaard *et al.*[17] The reasons for more ADRs being reported for boys than for girls remain to be explored. There is evidence that boys are prescribed medicines more often than are girls,[8] and prescribing patterns have been associated with reporting of ADRs,[29] but the sex differences might also reflect an increased susceptibility to develop ADRs on drug exposure in boys compared with girls.

ADRs that demonstrated sex differences in the present study were suicidality and aggressiveness, both more common in boys than in girls. For suicidality, a particularly important reaction, there were 12 ADRs concerning boys whereas only 1 ADR for a girl, and the reactions were associated with treatments with SSRI, isotretinoin, montelukast, centrally working sympathomimetic drugs, and an antibiotic (acne indication). These sex differences were statistically significant. For isotretinoin, an association with suicidality has been discussed previously, although it was recently concluded by Sundström *et al.* that the condition of severe acne itself constitutes a risk for suicidal behavior.[30] Treatment with SSRI has been associated with suicidality and has received much attention after a warning was issued by the US Food and Drug Administration in 2004.[31–33] For the centrally working sympathomimetics, a possible association with suicidality is presently being discussed [34] but has not been established. Montelukast

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Table 4. Reported psychiatric adverse drug reactions in children in different age groups (vaccines excluded)

	Psychiatric reactions per age group (*n* (%))			
	1–23 months	2–5 years	6–12 years	13–18 years
Agitation	3 (7.3)	13 (16.5)	7 (4.0)	4 (2.6)
Anxiety	8 (19.5)	3 (3.8)	17 (9.6)	20 (12.9)
Affective disorder	0	6 (7.6)	23 (13.0)	32 (20.6)
Personality disorder	5 (12.2)	7 (8.9)	19 (10.7)	7 (4.5)
Sleep disorder	11 (26.8)	20 (25.3)	31 (17.5)	22 (14.2)
Irritability	4 (9.8)	2 (2.5)	7 (4.0)	3 (1.9)
Aggressiveness	6 (14.6)	15 (19.0)	37 (20.9)	11 (7.1)
Hallucination	1 (2.4)	10 (12.7)	19 (10.7)	11 (7.1)
Suicidal conditions	0	0	1 (0.5)	12 (7.7)
Other	3 (7.3)	3 (3.8)	16 (9.0)	33 (21.3)
ADRs / ICSRs	41 / 25	79 / 59	177 / 120	155 / 117

ADRs, Adverse Drug Reactions; ICSR, Individual Case Safety Reports.
One ICSR may contain more than one reaction.

has been previously associated with suicidality but was only suspected in one ICSR concerning suicidality in the present study.[35,41] Our results regarding sex differences represent a novel finding that has not previously been described and may serve to generate new hypotheses regarding drug safety in children.

The psychiatric reactions also display age differences. Reactions such as agitation, anxiety, or sleep disorder were all reported more frequently in infants and preschool children. The reason for these age-related differences and also the difference in psychiatric reactions between adults and children is not known, but one may speculate that certain psychiatric reactions may reflect somatic adverse reactions of which the child is not capable of communicating verbally. Therefore, if a psychiatric adverse reaction is suspected in young children, increased attention of the possible presence of somatic adverse reactions is suggested.

Off-label drug use was associated with a significantly higher number of reported serious adverse reactions in the present study, and the most common off-label drug use was drug use not indicated to the age of the children. The clinical significance of drug use off-label is controversial and not fully understood.[2,8,9,36–39] The finding that off-label drug use is associated with a higher number of serious ADRs in the present study is important and may indicate that off-label drug use constitutes a safety concern in children. For assessment of the safety profile of a drug, it is important to consider tissues and organs under continuous development such as the skeleton, the brain, and the reproductive system, and therefore, it is important to generate documentation for the appropriate age groups.

Among drugs frequently associated with psychiatric ADRs, montelukast has previously been associated with nightmares, anxiety, and aggressiveness.[21] In the present study, as much as 10.0% of the total number of ICSRs concerned montelukast. Several different reactions were reported, such as hyperactivity, personality disorder, sleep disorder, and aggressiveness, and they had high rates of dechallenge and rechallenge. Our data and previously published studies[21,40] may indicate safety issues for montelukast, and therefore, a careful assessment of the risk–benefit analysis is important. The centrally working sympathomimetic drugs, 8.7% of the ICSRs, also represent a group where psychiatric adverse reactions are frequently reported, as recently demonstrated in a Danish study and in the present study. The most frequent reactions for these drugs were, in the present study, aggressiveness, affective disorder and personality disorder. As for montelukast, the reactions displayed high rates of positive dechallenge and rechallenge. Despite this, symptoms of the underlying disease may interfere with symptoms of the ADRs and complicate the assessment of whether the symptoms represent an ADR or not. Inhaled glucocorticoids are also highly represented in the present study, with 6.5% of the total number of ICSRs. Psychiatric reactions have been shown to be frequently reported in association with treatment with inhaled glucocorticoids,[22] but the high number of ADRs in association with these compounds might be explained at least in part by extensive prescription of inhaled glucocorticoids.[29,41] Psychiatric reactions are also frequently reported for SSRI, as demonstrated recently,[31] and in the present study, aggressiveness, hallucination, agitation, sleep disorder, and suicidality were reported. For hallucination, three cases were reported for SSRI, all of which were considered serious and two of which had positive dechallenge. Similar findings were seen for the centrally working sympathomimetics. Reports on hallucinations in association with SSRI therapy[42,43] as

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well as with the centrally working sympathomimetic drugs[44,45] have been published previously, and awareness of this unusual but potentially severe adverse reaction is important because it may be mistaken for a symptom of the disease.

The main limitation with the present study is that SWEDIS is built on a spontaneous reporting system, and underreporting is an issue in such systems. Therefore, true risks of ADRs cannot be estimated from our data. Details regarding reporters (pediatricians/general practitioners etc) are not included in the current analysis, but these details could have influenced assessment of adverse reactions. Nevertheless, spontaneous reporting systems still represent an important means to identify safety signals, not least in vulnerable populations such as the pediatric population, and the reporting frequency in Sweden is relatively high in the international perspective.[3,46] The main strength with the present study is the large number of reports included during a long period and the thorough characterization.

In conclusion, we demonstrate that psychiatric adverse reactions in the pediatric population have been reported for a wide range of reactions and drugs, and serious adverse reactions are reported more frequently after off-label drug use than after drug use according to the *Swedish Physician's Desk Reference*. The adverse reactions in the present study displayed age and sex differences, including a higher rate of suicidal reactions and aggressiveness in boys. Increased awareness of psychiatric adverse reactions would be beneficial for montelukast, centrally working sympathomimetics, inhaled glucocorticoids, and SSRI. More studies are needed to cast light on drug safety in the pediatric population.

CONFLICT OF INTEREST

The sponsor of this project had the right of final editing and/or approval of the manuscript submitted.

KEY POINTS
- Psychiatric ADRs are reported for many different drugs both used for psychiatric and somatic indications,
- Psychiatric ADRs display age and sex differences,
- Off-label drug use is common and associated with more serious ADRs in the present study.

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