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ORIGINAL RESEARCH ARTICLE

Psychiatric Disorders and Montelukast in Children: A Disproportionality Analysis of the VigiBase®

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Abstract

Introduction In 2008, the US FDA issued an alert about an increased risk of psychiatric events associated with montelukast. Recent national pharmacovigilance analyses in Sweden, France and Spain detected a potential increase in reporting risk of the association.

Aim Our objective was to analyse spontaneous reports of psychiatric events in children and adolescents worldwide treated with montelukast.

Methods We conducted a retrospective analysis of Individual Case Safety Reports (ICSRs) recorded up to 1 January 2015 in the World Health Organization (WHO) database (VigiBase®), in which montelukast was associated with 'psychiatric disorders'. We used the Bayesian Confidence Propagation Neural Network (BCPNN) approach for signal generation.

Results A total of 14,670 ICSRs for montelukast were recorded, of which 2630 corresponded to psychiatric disorders in people aged <18 years. The main symptoms reported for infants (aged <2 years) were sleep disorders, for children (aged 2–11 years) the main symptoms were depression/anxiety, and for adolescents (aged 12–17 years) they were suicidal behaviour and depression/anxiety. Suicidal behaviour was over-represented in all age groups with information component (IC) values that reached 5.01 in children and 3.85 in adolescents. Unexpectedly, completed suicides were reported more frequently for children (IC: 3.15; IC025: 1.98) than for adolescents (IC: 3.11; IC025: 2.61) or the total population (IC 1.95; IC025: 1.73).

Conclusions Neuropsychiatric disorders as side effects of montelukast were more frequently reported for children than for adults. Infants and children seem to be more prone to sleep disturbances, whereas adolescents present symptoms of depression/anxiety and psychotic reactions more often. Suicidal behaviour and completed suicide appear to be more frequently reported than previously thought in practice. Risk management plans and epidemiological studies are needed to quantify the risk. Practitioners should be aware of the risk of neuropsychiatric events associated with montelukast use, and should advise the patient and report new cases.

Key Points

Since the US FDA alert in 2008, psychiatric events associated with montelukast use have been reported worldwide.

Psychiatric disorders associated with montelukast use, especially suicidal behavior, have been reported more often than expected in children and adolescents during the last decade.

Prescribers must be aware of the neuropsychiatric risk involved, advise the patient and report new cases.

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1 Introduction

Montelukast is a selective leukotriene type I receptor antagonist that has been available since 1998. It is used as preventive medicine to reduce the frequency of asthma exacerbation in children with mild–moderate asthma. The use of montelukast is more frequent in children than in adults because it has been authorized by the US FDA and national European regulatory agencies to relieve symptoms of rhinitis and asthma in young patients, from 6 months of age in perennial allergic rhinitis or 12 months of age in those requiring chronic treatment of asthma and in other clinical situations. Furthermore, the pharmaceutical forms of montelukast—granules and chewable tablets—are easier for children to take than inhaled anti-asthmatic drugs.

In 2008, the FDA issued a warning about an increased risk of neuropsychiatric events associated with the use of antileukotriene agents: montelukast and zafirlukast (leukotriene receptor antagonists) and zileuton (leukotriene synthesis inhibitor) [1, 2]. The FDA and the manufacturers reviewed all the information from the clinical trials and some post-marketing cases [3–6] and issued an update in the 'precautions' section of the prescribing information to include neuropsychiatric events reported in patients using these products [7]. The European Medicines Agency (EMA) adopted a modification of an agreed 'Paediatric Investigation Plan' for montelukast in October 2009, and national regulatory agencies introduced neuropsychiatric events as rare adverse reactions in the post-marketing experience [8, 9].

A recent quantitative analysis by Wallerstedt et al. [10] and Bygdell et al. [11] of the Adverse Drug Reaction Swedish database (SWEDIS) also detected a potential increased reporting risk of neuropsychiatric events in children. The same tendency was detected in other national pharmacovigilance databases such as the 'Association française des centres régionaux de pharmacovigilance' [12] and the 'Sistema Español de Farmacovigilancia' [13].

Since 1978, the Uppsala Monitoring Centre (UMC), a World Health Organization (WHO) Collaborating Centre, has been the focal point of independent global pharmacovigilance. VigiBase® is the largest and most comprehensive data resource in the world; it is developed and maintained by the UMC on behalf of the WHO.

As of September 2015, a total of 122 countries have joined the WHO Programme for International Drug Monitoring [14]. VigiBase® is the name of the WHO Global Individual Case Safety Report (ICSR) database; it consists of reports of adverse reactions received from member countries at least quarterly. VigiBase® is continuously updated with incoming ICSRs. Currently, the database stores more than 11 million records and has been used for the early detection of signals, updating Product Safety Update Reports (PSURs) and comparison of reports in company databases [15].

The main objective of this study was to analyse the profile of psychiatric events in the paediatric population treated with montelukast reported to the WHO Global ICSR database. The hypothesis was that there is an increased association reported worldwide between the use of montelukast and psychiatric disorders in children and adolescents than in the global population (including adults).

2 Methods

We carried out a retrospective analysis of spontaneously reported cases of adverse drug reactions (ADRs) from the international WHO global ICSRs database, VigiBase®.

ICSRs concerning montelukast use in individuals aged <18 years were preselected.

Eligible cases for the analysis were all ICSRs received up to 1 January 2015 in which montelukast (as a single or multiple ingredient in the R03DC Anatomical Therapeutic Chemical [ATC] group, whether suspicious or not) was associated with the System Organ Class (SOC) term 'psychiatric disorders', which is the most frequently notified SOC term for montelukast, especially in people aged <18 years. The percentage of notifications with the association psychiatric or nervous disorders and montelukast was evaluated. The paediatric population was classified into three main groups: infants (aged <2 years); children (2–11 years) and adolescents (12–17 years), according to ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) Topic E 11 [16]. The association with psychiatric disorders was explored for other anti-asthmatic drugs such as R01AD corticosteroids and R03A adrenergic inhalants in absolute numbers.

The information contained in case reports consists of administrative data and information about patients, ADRs and medication. ADRs are coded according to MedDRA® (the Medical Dictionary for Regulatory Activities). These medical terms are classified in five levels of structural hierarchy [17]: SOC, high-level group terms (HLGT), high-level terms (HLT), preferred terms (PT) and lowest-level terms (LLT).

MedDRA® also includes Standardised MedDRA Queries (SMQ), which are collections of MedDRA® terms consistent with a description of a clinical syndrome associated with an adverse reaction and a drug exposure, useful for global searches. For further analysis, the PT included within HLGTs shown below were reclassified into four

main categories (not all terms were included in an specific SMQ, and it was indicated):

- *Depression/anxiety* Including the PT from the following HLGTs: 'Anxiety disorders and symptoms', 'Depressed mood disorders and disturbances' and 'Mood disorders and disturbances'. This group was identical to the SMQ for montelukast and paediatric population searches.
- *Psychosis and psychotic disorders* Including the HLGT in relation with the PT, typically medication induced: 'Deliria (including confusion)', 'Disturbances in thinking and perception' and 'Cognitive and attention disorders and disturbances'.
- *Suicide/self-injury* Including PT from the HLGT: 'Suicidal and self-injurious behaviour'. This group was identical to the SMQ, excluding 'intentional overdose'.
- *Sleep disorders* No SMQ was available for this category. The HLGT included was 'Sleep disorders and disturbances'. This HLGT includes HLTs that cover all aspects of sleep disorders.

The ICSRs were classified as serious or not serious, and unknown when this information was missing.

The UMC performs a statistical analysis of the old and new ADR reports every quarter with a Bayesian Confidence Propagation Neural Network (BCPNN) [18]. This method is effective in identifying possible signals, and it was applied in this study because it allows the inclusion of low count values and the results can be calculated despite missing data. The analysis provides the strength of dependency between a drug and an ADR and is calculated using a logarithmic measure of disproportionality called the 'Information Component' (IC) [19]. The IC gives a measure of the disproportionality between the expected and the reported rate of ADRs for a given drug. An IC value of 0 indicates drug–ADR combinations for which the number of observed cases is the same as that which might be expected from the overall reporting in the dataset. Positive values (IC >0) represent combinations reported more frequently, and negative values more infrequently, than expected. Confidence intervals of the IC are calculated to account for sampling variability. An IC025 with positive lower 95 % confidence limit (95 % low) indicates a statistically significant disproportionality between the expected and the reported rate for a drug and an ADR. A high IC value in addition to a lower 95 % confidence limit denotes a strong association between the drug and the ADR [20] in the database.

The IC and IC025 were calculated by quarters for each age group, and adult cases were also considered for comparative evaluation. The time to onset of the events (mean, median, minimum and maximum values), the outcome (recovered, recovered with sequelae, recovering, not recovered, unknown) and the de-challenge effect were analysed. ES is a member of the Signal Review Panel of the UMC, and the authors accepted the conditions for use stated in the UMC caveat document [21].

3 Results

A total of 10,305,720 ADR reports were registered in VigiBase® up to 1 January 2015: 1,023,414 ICSRs involved people aged <18 years, and 97,222 ICSRs reported psychiatric disorders. The total number of ICSRs for montelukast was 14,670. The most common SOC reported for montelukast was 'psychiatric disorders', which were reported in 5277 ICSRs (36 % of all ICSRs for montelukast), of which 2630 (50 % of psychiatric disorders for montelukast) corresponded to individuals aged <18 years (114 ICSRs aged <2 years; 2007 ICSRs aged 2–11 years; 509 ICSRs aged >11 years). The reports came from 49 countries.

The second most frequently reported SOC term for montelukast was 'nervous system disorders', which accounted for 24 % of all ICSRs for the drug (3460 ICSRs, of which 1225 corresponded to individuals aged <18 years). Altogether, effects on the central nervous system (CNS) accounted for 60 % of all ADRs reported for montelukast.

The psychiatric disorders reported in relation to other anti-asthmatic drugs were as follows. As at 1 January 2015, a total of 102,480 ICSRs had been notified for corticosteroids (R01AD), only 7 % of which were related to psychiatric disorders. For adrenergic inhalants (R03A), 97,951 ICSRs were reported in the same period, and only 7 % were related to psychiatric disorders.

Boys were over-represented (1651; 63 %) compared with girls (938; 36 %; 2 % unknown) in the paediatric age range (<18 years). The percentage of male versus female sex for each age group was as follows: infants 63/37; children 67/32 and adolescents 48/52. This contrasts with the male/female proportion in adults (29/70).

The most common HLGT in the 'psychiatric disorders' SOC category associated with montelukast in the paediatric population (<18 years) were 'Personality disorders and disturbances in behaviour' (955; 36 %), 'Sleep disorders and disturbances' (957; 36 %), 'Mood disorders and disturbances' (955; 36 %), 'Anxiety disorders and symptoms' (823; 31 %), 'Suicidal and self-injurious behaviours' (674; 26 %) and 'Depressed mood disorders and disturbances' (608; 23 %). All the HLGTs of the 'psychiatric disorders' SOC category are described in Fig. 1. As most of the ICSRs included more than one ADR, the number of ADRs is higher than the number of ICSRs, and the proportions

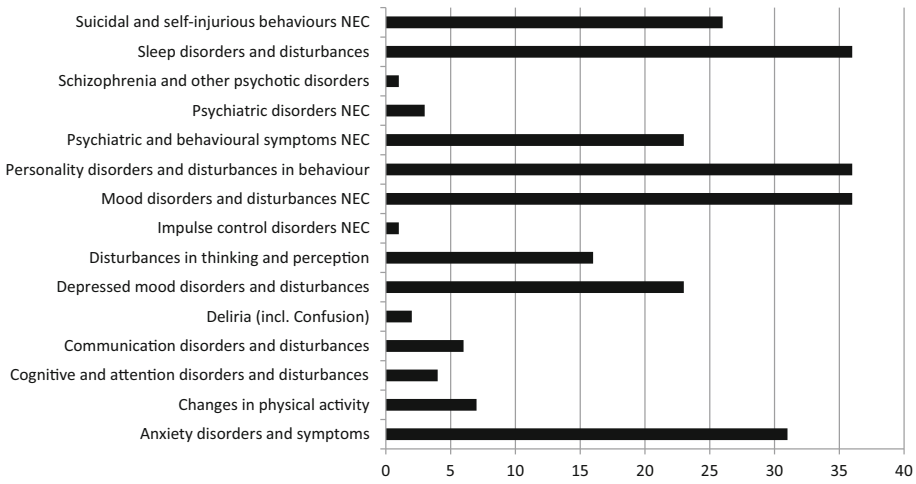

Fig. 1 Percentage of the HLGT found in the Psychiatric Disorders SOC category associated with montelukast and analyzed from the ICSR reports in <18 years individuals (HLGT with >1 %). *NEC* Not elsewhere classified is a standard abbreviation used to denote groupings of miscellaneous terms that do not readily fit into other hierarchical classifications within a particular SOC. *HLGT* High-Level Group Term, *SOC* System Organ Class, *ICSR* Individual Case safety Report

refer to the total number of ICSRs considered for this analysis (2630 ICSRs for psychiatric disorders in people aged <18 years).

The percentage of serious cases in each group is shown in Annex 1 (see the Electronic Supplementary Material [ESM] 1). There were 26 fatal cases with depression/anxiety involving all age groups, and 183 ISCRs including completed suicide, as shown in Annex 2 (see the ESM 2).

The total number of reports and the IC (IC025) values for the four topics in the different age groups are shown in the Annex tables 3–6 (see ESM 3). The temporal trend of the IC values for the four main topics and the different age groups were calculated for the period up to October 2013 and appear in Figs 2, 3, 4 and 5.

All topics reached IC values higher than zero for all paediatric groups after 2008 (when the first FDA signal was published [1, 2]) and continue to rise to date. There were

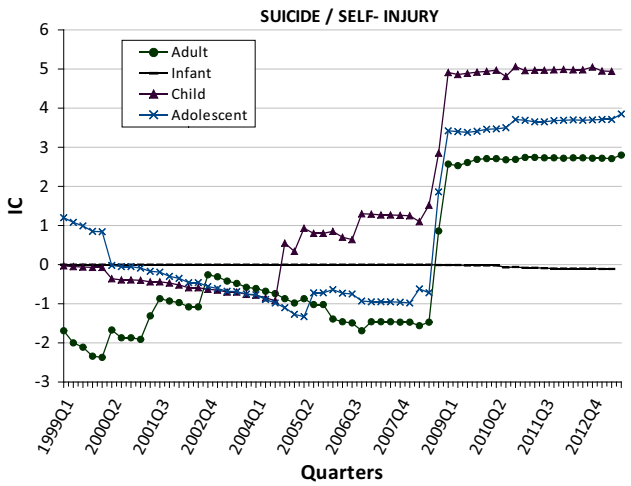

Fig. 2 IC values in suicidal behaviour (HLGT) up to 30 September 2013. *HLGT* high-level group term, *IC* information component, *Q* quarter

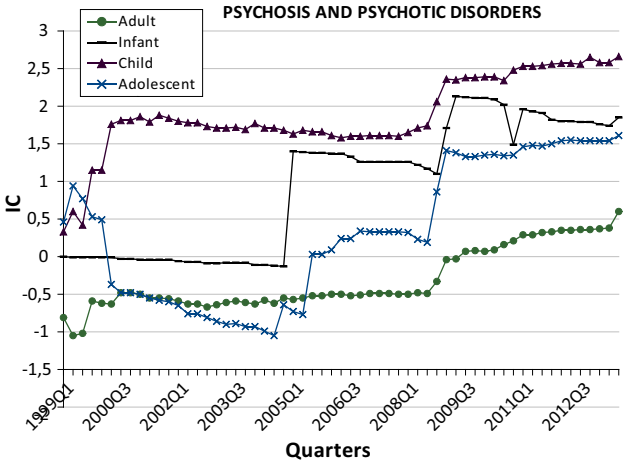

Fig. 3 IC values in psychotic disorders (HLGTs: 'Deliria', 'disturbances in thinking and perception', 'Cognitive and attention disorders and disturbances') up to 30 September 2013. *HLGT* high-level group term, *IC* information component

significant differences between age groups. Children (2–11 years) had the highest IC values for 'Suicidal behaviour' and 'Sleep disorders', and 'Depressive and psychotic symptoms'. In all cases, the IC for paediatric populations was higher than for adults. Data corresponding to infants are difficult to analyse due to the low absolute number of reports, and IC values are therefore around zero or negative, except for 'Sleep disorders', where infant IC values are similar to those of the other paediatric groups.

IC values are much higher than expected for all groups as from the year 2000, 2 years after introduction to the market, and increased significantly after the FDA signal. For suicidal behaviour, the IC increased in 2005 and rose further in 2008.

ICSRs reporting 'Sleep disorders' are abundant (746 cases), and the IC is higher in all paediatric groups than in adults, with children aged 2–11 years being most

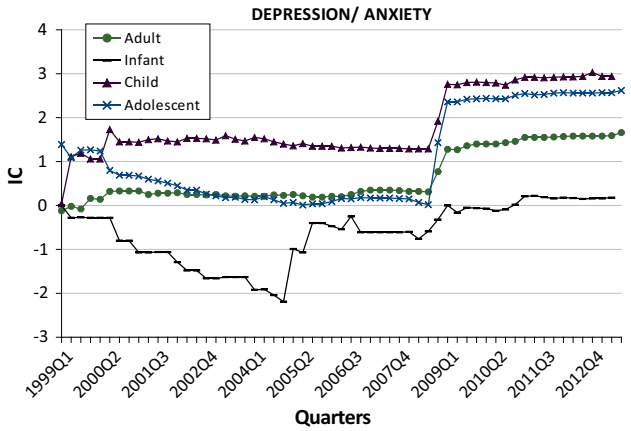

Fig. 4 IC values in anxiety/depression (HLGTs: 'Anxiety disorders and symptoms', 'Depressed mood disorders and disturbances', and 'Mood disorders and disturbances') up to 30 September 2013. *HLGT* high-level group term, *IC* information component

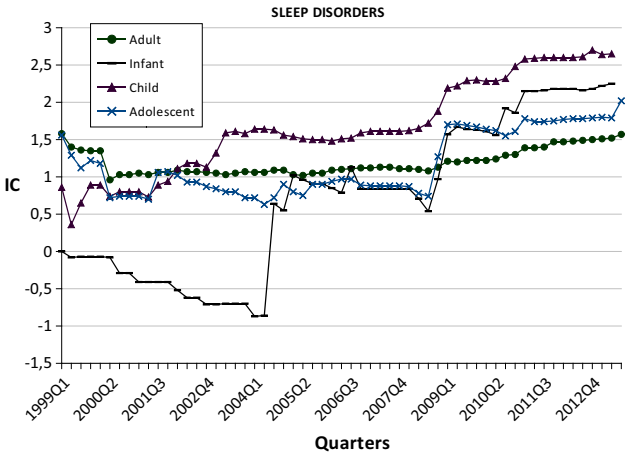

Fig. 5 IC values in Sleep disorders (HLGT: 'Sleep disorders and disturbances') up to 30 September 2013. *IC* information component, *HLGT* High-Level Group Terms, *Q* quarter

frequently involved. For this group, IC values are higher than zero as from 1999 and increasing steadily. Sleep disorders is the only HLGT that has been reported for infants (<2 years) in numbers that allow for interpretation, and the IC value reached 2.65 in this group. 'Sleep terror' and 'nightmare' were the PTs with the greatest disproportionality: IC 6.51 and 4.54, respectively. The most frequent concomitant medications were salbutamol 14 %, fluticasone 9 %, cetirizine 6 %, budesonide 6 % and fluticasone propionate/salmeterol 5 %.

Depression/anxiety was reported in as many ICSRs as was sleep disorders, despite not being as widely recognized. The IC was similar for children and adolescents, but it was almost twice the IC for adults. For children (aged 2–11 years), the IC values were over zero as from the year 2000, and for adolescents it increased dramatically after the publication of the signal in 2008 and continues to be high.

Psychosis and psychotic disorders are difficult to diagnose in paediatric populations but have been consistently reported since the year 2000, especially for children (aged 2–11 years). The IC for adolescents rose sharply in the year 2009 after the signal, and has been increasing since then.

The data for 'Suicide/self-injury' have been carefully reviewed up to 1 January 2015, with special attention given to the ICSRs that reported 'completed suicide'. In the global WHO database, 6722 ICSRs are for the 'Suicidal and self-injurious behaviours' HLGT for all drugs in the paediatric population. Of these, 10 % (674) correspond to a single drug: montelukast. The HLGT 'Suicidal and self-injurious behaviours' related to montelukast included several PT: Suicidal ideation (447; 66 %), Suicide attempt (95; 14 %), Intentional self-injury (60; 9 %), Completed suicide (56; 7 %), Self-injurious ideation (44; 7 %), Self-injurious behaviour (44; 7 %) and Suicidal behaviour (27; 4 %). The most frequent concomitant drugs were inhaled corticosteroids (budesonide, mometasone) and beta-adrenergic agents, at 2 % to 27 %, respectively in children.

For the 'Suicidal and self-injurious behaviours' HLGT, the PTs 'Completed suicide' (82 %) and 'Suicide attempt' (78 %) were more frequently reported for adolescents, and suicidal ideation (66 %) were more frequently reported for children.

Annex 2 (see the ESM 2) shows the total number of ICSRs, the number of ICSRs of positive de-challenge cases, the number of positive re-challenge cases, the fatal cases and the IC in each age group. It highlights that suicidal ideation, aggression, suicide attempt or depression account for 52, 44, 22 and 48 % of ISCRs with positive de-challenge, respectively.

Data on duration of treatment, onset of reaction and recovery are presented in annexes 7 and 8 (see ESM 4). Information is limited to approximately one-third of the cases. The median time to onset varies from hours or a few days for sleep disorders and psychotic disorders, to one to several weeks for depression disturbances. For the suicidal category, the median time to onset is much higher, ranging from months to years.

Data on the 'recovering' situation are also displayed in annexes 7 and 8 (see ESM 4); the information about recovery is sparse (20–50 % of cases) and when known, most patients recovered after discontinuing the medication.

After reviewing the reports and excluding duplicates (seven ISCRs), there were 35 cases of 'Completed suicide' associated with montelukast. The most common concomitant medication in 'Completed suicide' ICSRs were corticosteroids (budesonide, fluticasone, fluticasone/salmeterol; ten ICSRs) and beta-adrenergic agonists (salbutamol; seven ICSRs). For 'Completed suicide' ICSRs, the

duration of treatment was reported in 11 cases, varying from less than a year in two cases to more than 2 years in nine ICSRs.

4 Discussion

Once a signal has been detected, it needs to be followed up, and further analysis of the database can provide strength and new information to be considered [22]. The term 'Psychiatric disorder' is the most frequent SOC reported in relation to montelukast use (36 %) in the VigiBase® database, followed by the SOC 'CNS' (24 %), which, when combined, account for 60 % of all ADRs reported for this drug. This was described in 2012 by Bygdell et al. [11], who analysed ADRs in the paediatric population reported over a 10-year period in the Swedish ADRs database, and described the psychiatric disorders associated with all kind of drugs used in children. Montelukast was included in that analysis, but cases were few, and the authors could not show relevant age and sex differences in the association of montelukast with psychiatric disorders. However, in that analysis, the association between psychiatric disorders and montelukast was reported to VigiBase®, from 49 different countries, more frequently than with other anti-asthmatic drugs such as adrenergic inhalants and corticosteroids. These findings strengthen the signal.

The present study about montelukast and psychiatric disorders analyses the largest collection of data on ICSRs. The analysis was performed grouping the ICSRs into four main groups for two reasons: the ICSRs include little information about the clinical record of the patient, and it is difficult to establish a confirmed diagnosis, so some of the diagnoses could overlap.

Differences exist in the frequency of ICSRs reported according to age groups. The main symptoms reported for infants (aged <2 years) were sleep disorders, whereas for children (aged 2–11 years), it was depression/anxiety and sleep disorders, and for adolescents (aged 12–17 years) they were depression/anxiety and suicidal behaviour. Suicidal behaviour was over-represented in all age groups, with IC values > 3 in all cases. No clear sex differences were found.

Sleep disorders are well known and are recognized in Patient Information Leaflets (PILs) and the Summary of Product Characteristics (SmPC) [7–9]. The IC value was > 2 in all age groups, and was higher in children aged <11 years than in adolescents. Psychiatric symptoms are difficult to evaluate in children aged <2 years of age and so few ICSRs are reported to the database. Nevertheless, sleep disorders are also well reported and acknowledged for this group, whereas the paucity of data and the difficulties of interpretation for other symptoms prevent any analysis for infants aged <2 years.

'Sleep terror' and 'Nightmare' were the most frequently reported psychiatric ADRs, as in the analysis of the SWEDIS database during the period 2001–2010 [11]. Anti-asthmatic drugs are administered to control nocturnal asthma symptoms; however, most of them produce sleep disturbances. It is therefore difficult to evaluate causality, because these drugs are commonly used together [23].

The 'Depression' category presents an IC twice as high for children as for adults. This IC value has been high for children (aged 2–11 years) since 1998 and had increased from 1 to 2.8 in 2009, and has continued to increase slightly since then. Asthma has been associated with depression, and it is difficult to evaluate the possible contributing factors: the influence of the disease, the concomitant presence of depression and the role of the drug in the presence of symptoms [24, 25]. Nevertheless, the high and stable association over time between the use of montelukast and the presence of depressive/anxiety symptoms in children needs to be seriously considered and cannot be ruled out.

Conversely, psychotic symptoms are quite rare in the paediatric population. There is a strong association between the use of montelukast and reports of psychotic symptoms, especially in those aged 2–11 years (IC: 2.66) and in adolescents (IC: 1.61). IC values have increased steadily since 2008. The corresponding IC value for adults is 0.6. This disproportion points towards a causal relationship and a higher predisposition in children. The fact that montelukast is more widely used in children than in adults might influence the notification rate of ADRs, but the difference is high enough to consider a higher reporting risk of psychotic side effects in young children.

The data on 'suicidal behaviour' are striking. IC values reached 5.01 in children (aged 2–11 years) and 3.85 in adolescents, and have been increasing, especially in adolescents. The IC value for adults is lower (2.8). The category suicidal behaviour includes several PTs in relation with self-injury and attempted/completed suicide. We performed a further analysis of the 35 ICSRs reporting completed suicides, which was more frequently reported for children (aged 2–11 years; IC: 3.15) than for adolescents (IC: 3.11) and the total population (IC: 1.95). In VigiBase®, the suicide and self-injury terms were labelled as serious in all the age groups for 85–90 % of cases. Furthermore, there were 26 fatal cases with depression involving all age groups, but there were seven times more completed suicide reports. The positive de-challenge in ideation, attempted suicide or self-injurious behaviours, or the positive re-challenge in a few cases, support the urgent need for more studies on the magnitude of this association. Several epidemiological studies have analysed the association between chronic diseases, and asthma in particular, with suicidal behaviour [26]. Only a few studies have

focused on individuals aged <18 years [27, 28]. A recent review of the evidence from observational data supports the hypothesis of an association between asthma and suicide-related behaviour (ideation, attempts and completion) in the general population. As Iessa et al. [29] concluded, "epidemiological studies, with more objective measures and larger sample sizes, adjusting for a wider scope of suicide-related confounding factors (e.g. comorbidities), and with a longitudinal design, are needed for a more conclusive answer". Nevertheless, the high disproportion of reports involving children, especially when compared with the reports for adults, the positive de-challenge and re-challenge of the drug in some cases, and the fact that the prescriber associated the unexpected outcome with the drug suggests that the suicidal behaviour cannot be based solely on this possible association with the disease.

The time from exposure to ADR was described as less than 1 week in the Swedish [10] analysis, but the results of this analysis in VigiBase® showed the time to onset varied from days to years: a few days in relation to sleep disorders, agitation and nervousness, and months to years in relation to depression and suicide-related behaviour.

The IC values in the paediatric population could be influenced by several biases. On the one hand, montelukast is more frequently used in this population than in adults and thus more reports for children would be expected. However, the IC values for adults are also consistently high for all four categories ('Depression/anxiety', 'Psychosis and psychotic disorders', 'Suicide/self-injury' and 'Sleep disorders'). Furthermore, IC value is a measure of disproportionality that is compared against each age group; therefore, despite the absolute numbers of cases, the IC value indicates a higher reporting risk of ADR and the drug.

Another bias, especially related to suicidal behaviour reports, may be the well-known presence of sleep disorders, which could lead to infra-notification, against the dramatic nature of suicidal behaviour, which could lead to higher notification. Furthermore, sleep disorders are common and well acknowledged with montelukast, and this could influence the causality association (a form of notoriety bias) [30]. However, the IC for suicidal behaviour is very high, as it is for adults. Thus, although this bias cannot be completely ruled out, it would not substantially change the interpretation of the data.

IC values have risen since the FDA warning in 2008. That warning was based on the re-analysis of the clinical trials data and some post-marketing cases. Opinions between the health authorities, FDA and EMA, and the prescribers are currently diverse [31]. In 2014, the FDA analysed post-marketing cases in the paediatric population and maintained the warnings and precautions in the Labeled Safety issues for prescribers: "Patients and prescribers should be alert for neuropsychiatric events. Patients should be instructed to notify their prescriber if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment with montelukast sodium if such events occur" [32]. The current analysis goes further and is based on spontaneous reports from all over the world after many years of post-marketing. In this regard, the analysis reinforces the cautionary communication from the FDA and may provide more explanations on the differing susceptibilities between age groups.

It is difficult to link the pharmacological action of montelukast with the development of neuro-psychiatric symptoms. Montelukast is a specific leukotriene type I (CysLT1) receptor antagonist [33]. The distribution of the Cystenil receptors LT1 and LT2 differs, and only CysLT2 receptors are present in the CNS, whereas CysLT1 are distributed in lung smooth muscle cells, interstitial lung macrophages and the spleen. In fact, the affinity of montelukast for the CysLT2 receptor of the brain is very low [34]. Currently, there is no biological explanation for direct effects of montelukast on the CNS.

4.1 Strengths and Limitations

The analysis of spontaneous ADR reports has several limitations as well as clear strengths. The goal of the spontaneous reporting system and the analysis of data collection in VigiBase® is clearly defined: to look for signal generation and not for quantification of risks, as the data do not allow for a calculation of true frequencies. This system allows the generation of new hypotheses and new ways to study the true association adjusting for confounding factors. The absolute number of reports cannot be directly linked to the prevalence of the ADR in a given population; this database is useful to explore the disproportionality of ADR reports for a drug, and IC values give information on associations and risks, more than on causality or prevalence changes.

Confounding biases are also possible in the analysis. Montelukast is more commonly used in children than in adults, so the probability of receiving more reports on the paediatric population is also higher. Furthermore, sleep disorders are common, whereas suicidal behaviours are rare, possibly prompting a higher reporting rate. In addition, asthma has been linked with suicidal behaviour, although not definitively, and the concomitant cause cannot be ruled out completely. Finally, the FDA alert prompted a sudden high level of reporting of suicidal behaviours in patients receiving antileukotriene agents.

A major drawback of this paper is that it does not report anything regarding physical or psychiatric conditions or disorders in the children of this cohort. Obviously, if the patient has an existing psychiatric diagnosis, this is critical

information to have before attributing a psychiatric effect to a medication. Moreover, the diagnosis of psychiatric disturbances is difficult in young children, and one must be cautious in the interpretation of some psychiatric disorders according to MedDRA® codes.

However, this analysis of VigiBase® also has several strengths. The data are collected from sources all over the world and represent cases that individual physicians consider sufficiently important to report them to the national and international pharmacovigilance system. These data reflect the use of anti-asthmatic drugs in real life, outside clinical trials and years after their introduction to the market. Few drugs outside the psychotropic agents display a main neuropsychiatric drug reaction such as montelukast.

IC values are a measure of disproportionality that is stable for a given pair of drug side effects, and within a population group (age, origin, etc.). Thus, the higher the IC value, the more frequent, and disproportionate, the report of the association. The IC values rose immediately after the FDA warning some 6 years ago, but instead of falling after the warning, the rate of reports of neuropsychiatric events for montelukast has steadily rising for all those years. The IC values for the association of montelukast with depression, psychotic symptoms and suicidal behaviour in the different groups of (paediatric) ages, are very high. Many well-known side effects for other drugs have IC values lower than those obtained in this study, and signals with much lower IC values have prompted intense actions from regulators, resulting in changes to authorization processes and information for professionals. For example, in November 1999, the association between Nimesulide and hepatotoxicity had an IC of 0.54 with ten ICSRs. The SmPC was modified in late 1999. In September 2000, infliximab and tuberculosis had an IC of 0.54 with four ICSRs. Consequently, the SmPC was modified in Europe. The signal was evaluated for 2 years and, in 2002, the IC was 4.32 (IC: 3.6–5.1). In April 1999, the IC for cerivastatin and rhabdomyolysis was 1.52 with seven ICSRs. The drug was withdrawn, but the signal was followed for 2 years. In August 2002, the CI was 4.7 (IC 95 %: 4.4–5.1) [35].

Therefore, despite the study limitations, this signal cannot be ruled out without further analysis of the association.

5 Conclusion

Psychiatric symptoms, especially sleep disturbances, are widely recognized as side effects of montelukast, and this information is given in the SmPC of the drug. The present study analysed the distribution of different types of psychiatric symptoms associated with the drug in different paediatric age groups. The data support the hypothesis that montelukast could be linked with a higher prevalence of neuropsychiatric symptoms than currently recognized, although the data and the methods cannot quantify it. The analysis also revealed that neuropsychiatric disorders are more frequently reported for children than for adults, and that there are differences between age groups. Infants and young children seem to be prone to sleep disturbances, whereas older children and adolescents present more cases of depressive and anxiety symptoms and psychotic reactions. Suicidal behaviour and completed suicide seem to be more frequently reported than recognized in practice.

As stated by the FDA, safety concerns have been raised regarding the increased risk of neuropsychiatric adverse events, including suicide and suicide attempts, with the use of montelukast. "However, there continues to be a lack of well-designed epidemiologic studies that can lead to the quantification of the suicide/suicide attempt risk level among patients using montelukast" [32]. De Boer [36] also highlights that this type of design does not allow for causality evaluation or quantification but is useful to indicate areas in which other types of pharmaco-epidemiological approaches are needed.

This database is useful to explore ADRs reported, and IC values give information on the disproportionality between cases reported and those expected in the database, more than on causality or prevalence changes. Other epidemiological methods should be applied to quantify the risk, to attempt to define the true differences in the age groups, adjusting for a wider scope of suicide-related confounding factors. Due to difficulties in investigating the risk of suicidal behaviour in children and adolescents, the most appropriate approach may be to combine various strategies, such as disproportionality analysis, risk management plans, epidemiological studies and even animal experimental studies. Meanwhile, prescribers should carefully evaluate the potential risks and benefits of continuing treatment with montelukast and should advise the patient and report new cases.

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Compliance with Ethical Standards

This study is based on data mining and interpretation of the largest database for drug safety in the world (the WHO-UMC VigiBase®) and was conducted in accordance with their higher standards. Therefore, the CONSORT, PRISMA, EVEREST, STARD or STROBE statements could not be applied, nor could the study be registered in a 'trial registration' database. The study did not identify any individual patient and involved multinational data, so no Ethical Review Board approval was required.

Statements This is an original study and has not been submitted to, or published by, in whole or part, any other journal.
The authors followed the WHO methodology for signal generation and the caveat document of the WHO collaborating Centre for International Drug Monitoring, the UMC (http://www.who-umc.org/DynPage.aspx?id=98082). Emilio Sanz Álvarez is a member of the WHO-UMC Signal Review Panel.

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