

PSYCHOTROPIC DRUGS USE IN ASMATHIC CHILDREN AND ADOLESCENTS IN THE NETHERLANDS DURING 1999-2006

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Abstract

Objective: To determine the association between asthma and the use of psychotropic drugs by focusing on whether the asthmatic children receive more often psychotropic drugs compared with non asthmatic children in the population based cohort design.

Data source : InterAction Database (IADB), drug dispensing data from Dutch community pharmacies (55 community pharmacies) in 1999 – 2006.

Study design: Children and adolescents aged 0 to 19 years in the study period (1 Januari 1999 to 31 Desember 2006) were divided into two groups; the index (asthmatic children and adolescents) and the reference (antibiotic children and adolescents) groups. We calculated the incidences of psychotropic drugs use (in both groups) and the incidence risk ratio (IRR).

Results: The incidences of psychotropic drug use were 0.058 cases/1000 person-days in index group and 0.048 cases/1000 person-days in reference group. The incidence risk ratio of anti psychotropic drug use was 1.21 (CI 1.18-1.29).

Conclusions : Asthmatic patients are 1.21 times more likely than non asthmatic patients to receive psychotropic drugs over the 8 years period in this study.

Background

The use of pharmacotherapy for mental disorders in children and adolescents varies widely across countries. Increased psychotropic medication prevalence for youth has been reported during the last decade in the UK, Germany, Italy, Denmark, and the Netherlands, as well as in the US. The prevalence of psychotropic drugs increased from 11.1 per 1000 in 1995 to 22.9 per 1000 in 2001 in the Netherlands.¹

Another research in the Netherlands found the prevalence of stimulants was 7.4/1000 in 1999 among 0-19 years old, followed by hypnotics/anxiolytics 6.9/1000 and antidepressants 4.4/1000.² A drug utilization study of antidepressant for children and adolescents in the UK in 1992-2001 found 55.7% from 93,091 prescriptions were tricyclic antidepressants (TCAs), 41.3% were selective serotonin reuptake inhibitors (SSRIs), and 2.9% were other ATDs.³ In Germany, ATD prevalence was 3.43 per

1000, Confidence interval (3.21-3.65) in 2000 and 3.74 per 1000 , confidence interval (3.25-3.97) in 2003.⁴ The comparison of psychotropic medication prevalence in youth in three countries (USA, Netherlands and Germany) in 2000 found the annual prevalence use of any psychotropic drugs was 6.7% in the USA, 2.9% in the Netherlands and 2.0% in the Germany. The antipsychotics prevalence was 0.76% (USA), 0.51% (Netherlands), and 0.34% (Germany). The stimulants prevalence was 4.3% (USA), 1.2% (Netherlands), and 0.7% (Germany). The prevalence of antidepressants was 2.7% (US), 0.5% (Netherlands), and 0.2% (Germany).⁵ Antiepileptic drug utilization in children from 1997–2005 in the Netherlands found the cumulative incidence of AEDs was 0.67 per 1000 children, and the prevalence 4.0 per 1000 children.⁶

Mauro Percudani et.al found the prevalence of anti depressants among

patients under 19 years old was 2.78 per 1000, 95% CI was 2.70-2.87. From 4252 patients received anti depressants, 2814 patients received one of the selective serotonin reuptake inhibitors, and paroxetine was prescribed to 1065 of those receiving antidepressants.⁷

In 2008, the American Academy of Pediatrics and the American Heart Association have been clarifying recommendations for children using stimulants because they found that children with heart conditions have a higher incidence of ADHD.⁸

Other common concern of the stimulants are growth suppression, overuse and inappropriate use of stimulants.^{9,10} Liver toxicity, pancreatitis, thrombocytopenia and polycystic ovary disease in girls is a concern with valproate and other anti-epileptic drugs used for mood stability in children.^{9,11} The DERP systematic review found several reports of increased suicidal thoughts and behavior for citalopram, paroxetine, sertraline, and venlafaxine, but not for fluoxetine.¹² In 2005, the FDA added black box warnings for suicidal precautions in children and adolescents taking all classes of antidepressants.

A wide range of pediatric psychiatric problems presents more commonly in children with asthma.^{13,14} Mental disorders, particularly anxiety and depression, frequently affect children and adolescents with a chronic somatic illness like asthma.

Several studies found a higher incidence of psychiatric disorder in asthmatic children. One longitudinal community-based study on asthma and panic in adults has been

published, which reported asthma increased the risk of panic attack.¹⁵

One possible mechanism to explain the association between asthma and panic is that asthma can be treated for a whole life and this situation may increase the anxiety level (may lead to panic) probably through dyspnea-induced fear conditioning and derangement of respiratory receptor set-point.^{16,17}

Ortega et.al found children with a history of asthma were more likely to have any anxiety disorder, simple phobia, separation anxiety, and overanxious disorder than children without a history of asthma.¹⁸ Villa et.al in assessment of anxiety disorder in asthmatic children found asthmatic children had a higher score of anxiety disorder compared to non asthmatic children.¹⁹ In 2001, a meta-analysis study was conducted by McQuaid. This study included 26 studies, which covering 4923 asthmatic children, age 4-19 years. He found that children with asthma had significantly more adjustment problems relative to a reference group. Asthmatic children had more adjustment problems relative to a reference group. An Increase in asthma severity associated with an increase in level of adjustment problems reflected children with severe asthma may be at risk and require a treatment intervention.²⁰

In Drug Utilization Study, children are considered to be asthmatic when they receive more than one prescription for an inhaled corticosteroid per year (beclomethasone, budesonide, and fluticasone).²¹ Inhalation therapy is the cornerstone of asthma treatment for children of all ages. Most of the children can be taught to effectively use inhalation therapy.²²

In the period of June 1984-October 2004, adverse effects of Inhaled Corticosteroid were reported in 89 children younger than 17 years of age. Of those children, psychiatric symptoms were found in 19 children. An association between the use of ICS and behavioral changes in young children was found in the Netherlands, and the most frequently reported are agitation and hyperactivity.²³

Objectives

Although many studies have suggested an association between asthma and mental health problems, little information is known about this association. The use of psychotropic drugs can be used as a proxy of the prevalence of mental health problems in interaction with the recognition of those problems in populations. We therefore expected a higher use of psychotropic drug use in asthmatic children.

In this study, we tested the hypothesis that psychotropic drug use in a population of asthmatic children was higher than that in a reference population consisting of age and sex matched children who had received at least one systemic antibiotic per year.

We examine the association between asthma and the use of psychotropic drugs by looking at whether the asthmatic children receive more often psychotropic drugs compared with non asthmatic children in the population based cohort design.

Methods

We conducted a prospective cohort study to evaluate the use of psychotropic drugs and the association between asthma and the

use of psychotropic drugs in children and adolescents.

Data Source

We analyzed drug dispensing data from Dutch community pharmacies (55 community pharmacies) using InterAction database (IADB), which controls prescription records of approximately 500,000 individuals since 1999. (www.IADB.nl). Information on patient's characteristics (anonymous identifier, gender, and date of birth) and medication (drug name, anatomical therapeutical chemical code, dosage, and dispensing date) are included in the database. The use of over-the-counter (OTC) drugs and in-hospital prescriptions are not included.^{24,25}

Study Period

1999-2006

Study Population, Index and Reference Group

As the study population, we selected all children and adolescent aged 0 to 19 years in the study period (1 January 1999 to 31 December 2006) according to the index/matched date. Those children and adolescents were stratified into four categories of age: 0-4 years, 5-9 years, 10-14 years and 15-19 years.

From our study population, we selected two groups, the index (asthmatic children and adolescents) and the reference (antibiotic children and adolescents) groups.

The index group (asthmatic children) was defined as all children and adolescents who had received at least two prescription of anti-asthmatic medications/year {(inhaled

glucocorticoids (R03BA) or salmeterol and other drugs for obstructive airway diseases (R03AK06) or formoterol and other drugs for obstructive airway diseases (R03AK07); The index date was defined as the date of the first prescription for Inhaled Corticosteroid (ICS) in the index group in the study period. The reference group was defined as all children and adolescents who had received at least one systemic antibiotic (J01) but did not receive inhalation corticoids at the matched index date. The matched index date was defined as the date (matched with the index date) of the starter of systemic antibiotic in the reference group. The patients who have used psychotropic drugs before the index date were excluded.

Data Analysis

The incidences of the use of psychotropic drugs (in both groups) were calculated as the number of new psychotropic drug users, divided by the number of patient-day of the patients at risk (Incidence density). Number of patient-days was measured from the index date/matched date up until either the date of the first prescription of psychotropic drugs, the last known date of that person in the database, or the end of the study period, whichever occurred first.

We compared the index and reference groups and calculated incidence risk ratio (IRR). 95% confidence interval of asthma prevalence and incidence of psychotropic drugs use were also calculated. All statistical analysis was performed using SPSS 16.0 for windows.

Table 1. The list of Psychotropic Drugs

ATC-code	Group
NO3A	Anti epileptics
NO5A	Anti psychotics
NO5B	Anxiolytics
NO5C	Hypnotics and sedatives
NO6A	Anti depressants
NO6BA	Centrally acting simpatomimetics

Results

A. Characteristic of study population

The total number of asthmatic children (an index group) is 10579 and the total number

of corresponding antibiotic children (a reference group) is 42316 (by matching age and gender with an index group).

Table 2. Age-gender distribution in asthmatic children and adolescents during 1999- 2006

Age Category	Gender		Sub total
	Male	Female	
0-4 years	3214(62%)	1963(38%)	5177
5-9 years	1549(59%)	1097(41%)	2646
10-14 years	894(55%)	735(45%)	1629
15-19 years	406(36%)	721(64%)	1127
Sub total	6063(57%)	4516(43%)	10579

Table 2 displays the distribution of asthmatic patients stratified by age and gender. During the year under study, there are more male patients (57%) than female patients (43%). The number of patients decreases over the increasing order of age categories in male and female. At the first of

age category (0-4 years), the number of patients is nearly twice as great in boys as in girls. But at the last age category (15-19 years), the number of girls is nearly two-fold than boys. The percentage of patients decreases over the increasing order of age in male but increases in female.

B. Incidence of psychotropic drug use

From 10579 asthmatic patients, 936 patients had received psychotropic drugs after the index date and 362 patients had received psychotropic drugs before the index

date. In antibiotic patients, from 42316 patients, 2563 patients had received psychotropic drugs after the matched date and 1633 patients before the matched date.

Table 3. Incidence of psychotropic drug use, Incidence Risk Ratio and 95% Confidence Interval

Psychotropic Drugs	Asthmatic Patients (index group)			Antibiotic patients (reference group)			Incidence Risk Ratio (95% CI)
	Tot cases	Total time (person-days)	Incidence (cases/1000 person-days)	Tot cases	Total time (person-days)	Incidence (cases/1000 person-days)	
Any Psychotropic's	936	16216404	0.058	2563	53512538	0.048	1.21(1.18 to 1.29)
NO3A (Anti epileptics)	39	17155312	0.002	110	55906641	0.002	1.16(0.78 to 1.67)

Table 3. Incidence of psychotropic drug use, Incidence Risk Ratio and 95% Confidence Interval (continuation from page 7)

Psychotropic Drugs	Asthmatic Patients (index group)			Antibiotic patients (reference group)			Incidence Risk Ratio (95% CI)
	Tot cases	Total time (person- days)	Incidence (cases/ 1000 person- days)	Tot cases	Total time (person- days)	Incidence (cases/ 1000 person- days)	
NO5A (Anti psychotics)	80	17110392	0.005	172	55836260	0.003	1.52(1.14 to 1.99)
NO5B (Anxiolitics)	310	16842554	0.018	869	55205533	0.016	1.17(1.02 to 1.33)
NO5C (Hypnotics and sedatives)	103	17104354	0.006	253	55786414	0.005	1.33(1.04 to 1.67)
NO6A (Anti depressants)	94	17104689	0.005	375	55631265	0.007	0.82(0.64 to 1.02)
NO6BA (Centrally acting simpatomimetics)	310	16922463	0.018	784	55216300	0.014	1.29 (1.12 to 1.47)

From 936 incident users of psychotropic drugs among asthmatic patients (table 3), 33% have received anxiolitics, 33% stimulants, 11% hypnotics/sedatives, 10% anti depressants, 9% anti psychotics, and 4% anti epileptics. Among asthmatic patients, the incidence of anxiolitics use and stimulants use were the highest, 0.018 cases/1000 person-days. The lowest incidence belongs to anti epileptics, 0.002 cases/1000 person-days.

From 2563 incident users among antibiotic patients 34% have received anxiolitics, 31% stimulants, 15% anti depressants, 10% hypnotics/sedatives, 7% anti psychotics, and 4% have received anti

epileptics. Among antibiotic patients, anxiolitics incidence was 0.016 cases/1000 person-days, followed by stimulants, 0.014 cases/1000 person-days and the lowest was anti epileptics, 0.002 cases/1000 person-days.

In table 3, the incidence risk ratio for any psychotropic drugs is 1.21 with 95% confidence interval 1.18 to 1.29. The highest Incidence risk ratio belongs to anti psychotics (1.52) followed by hypnotics/sedatives (1.33) and stimulants (1.29). The anti epileptics and the anxiolytics have a similar incidence risk ratio (1.16 and 1.17) respectively. For anti depressants, the incidence risk ratio is less than 1 (0.82),

Table 4. The most frequent psychotropic drug among incident users in asthmatic patients

Group of psychotropic	Atc-code	Name	Patients/group (%)
Anti epileptics	NO3AG0 1	Valproic acid	27/39 (69%)
Anti psychotics	NO5AD0 5	Pipamperon	26/80 (33%)
Anxiolitics	NO5BA0 1	Diazepam	182/310 (59%)
Anti depressants	NO6AA	Non-selective monoamine reuptake inhibitors	37/94 (39%)
	NO6AB	Selective serotonin reuptake inhibitors	48/94 (51%)
Centrally acting simpatomimetics	NO6BA0 4	Methylphenidate	306/310 (99%)

Among incident users in asthmatic patients, in anti epileptic drugs group, valproic acid was the most frequent prescribed drug (69%). The most frequent prescribed drug in anti psychotics was pipamperon (33%), diazepam in anxiolitics group (59%), temazepam (59%) in hypnotics

and sedatives group. and methylphenidate (99%) in a group of centrally acting simpatomimetics. In anti depressants group, 39% had received non-selective monoamine reuptake inhibitors, and 51% had received selective serotonin reuptake inhibitors.

Table 5. The most frequent psychotropic drug among incident users in antibiotic patients

Group of psychotropic	Atc-code	Name	Patients/group
Anti epileptics	NO3AG01	Valproic acid	54/110 (49%)
Anti psychotics	NO5AX08	Risperidone	87/172 (51%)
Anxiolitics	NO5BA01	Diazepam	518/869 (60%)
Hypnotics and sedatives	NO5CD07	Temazepam	148/253 (58%)
Anti depressants	NO6AA	Non-selective monoamine reuptake inhibitors	137/375 (37%)
	NO6AB	Selective serotonin reuptake inhibitors	210/375 (56%)

Table 5. The most frequent psychotropic drug among incident users in antibiotic patients

(continuation from page 9)

Group of psychotropic	Atc-code	Name	Patients/group
Centrally acting simpatomimetics	NO6BA04	Methylphenidate	783/784 (100%)

Among incident users in antibiotic patients, in anti epileptic drugs group, valproic acid was the most frequent prescribed drug (49%). The most frequent prescribed drug in anti psychotics was risperidone (51%), diazepam in anxiolitics group (60%), temazepam (58%) in hypnotics and sedatives group. and methylphenidate

(100%) in a group of centrally acting simpatomimetics. In anti depressants group, 37% had received non-selective monoamine reuptake inhibitors, and 56% had received selective serotonin reuptake inhibitors. As can be seen in table 4 and 5, stimulants were the most widely used psychotropic agents among 0-19 year-olds.

Table 6. Incidence of psychotropic drug use in non-selective monoamine reuptake inhibitors, selective serotonin reuptake inhibitors and stimulants, Incidence risk ratio and 95% CI

Group	Asthmatic patients			Antibiotic patients			IRR (95% CI)
	Total cases	Total person-days	Incidence	Total cases	Total person-days	Incidence	
NO6AA	37	17164696	0.002	137	55858639	0.002	0.88(0.59 to 1.27)
NO6AA09	21	17187815	0.001	79	55940978	0.001	0.87(0.50 to 1.41)
NO6AB	48	17151173	0.003	210	55803415	0.004	0.74 (0.53 to 1.02)
NO6AB05	20	17184769	0.001	96	55914796	0.002	0.68(0.39 to 1.10)
NO6BA04	306	16634515	0.018	783	55217227	0.014	1.29 (1.13to 1.48)

Note:

NO6AA: non-selective monoamine reuptake inhibitors

NO6AA09: Amytriptilin

NO6AB:selective serotonin reuptake inhibitors

NO6AB05: paroxetin

NO6BA04: methylphenidate

Amytriptilin was the most frequent prescribed drug in non-selective monoamine reuptake inhibitors, in asthmatic and antibiotic patients. In selective serotonin reuptake inhibitors group, the most frequent prescribed drug was paroxetine, and methylphenidate in stimulants. As can be seen in table 5, the incidence risk ratio for non-selective monoamine reuptake inhibitors was 0.88 and 0.87 for amytriptilin. The incidence risk ratio in selective serotonin reuptake inhibitors was 0.74 and 0.68 for paroxetine. The incidence risk ratio of methylphenidate was 1.29.

Discussion

A. The incidence of Psychotropic Drugs use

We found that during the eight years period, from 10579 asthmatic patients, 1298 patients have received psychotropic drugs (12%). From this number, 362 patients have received psychotropic drugs before the index date and 936 patients after the index date.

In reference group, from 42316 antibiotic patients, 4196 patients have received psychotropic drugs (10%). From this number, 2563 patients have received psychotropic drugs after the matched date and 1633 patients before the matched date.

From 936 incident users of psychotropic drugs among asthmatic patients (table 2), 33% have received anxiolytics, 33% stimulants, 11% hypnotics/sedatives, 10% anti depressants, 9% anti psychotics, and 4% anti epileptics. Among asthmatic patients, the incidence of anxiolytics use and stimulants use were the highest, 0.018 cases/1000 person-days. Stimulants were the most widely used psychotropic agents among 0-19

year-olds; these findings are in line with report from Netherlands about psychotropic medication in children.^{10,19} They found that the prevalence of stimulants was 7.4/1000 in 1999 among 0-19 years old, followed by hypnotics/anxiolytics 6.9/1000 and antidepressants 4.4/1000.

From 2563 incident users among antibiotic patients 34% have received anxiolytics, 31% stimulants, 15% anti depressants, 10% hypnotics/sedatives, 7% anti psychotics, and 4% have received anti epileptics. The incidence of anxiolytic use was 0.016 cases/1000 person-days, followed by stimulants, 0.014 cases/1000 person-days and the lowest was anti epileptics, 0.002 cases/1000 person-days. These findings were also in line with report from the Netherlands,^{10,19} but the stimulants stayed in the second position after anxiolytics, followed by anti depressants.

Findings in asthmatic patients and antibiotic patients are supported by another research from UK about the comparison of psychotropic medication prevalence in youth in three countries (USA, Netherlands and Germany) in 2000 but only for stimulants. The USA stayed on the top followed by The Netherlands and The Germany. In that report, the prevalence of stimulants in the Netherlands was 1.2%, followed by Anti Psychotics (0.51%) and anti depressants (0.50%).²³

The incidences of anti psychotics and anti depressants were low in both groups. The incidences of anti psychotics were 0.005 cases/1000 person-days (asthmatic group) and 0.003 cases/1000 person-days (antibiotic group). Anti depressants incidences were 0.005 cases/1000 person-

days (asthmatic group) and 0.007 cases/1000 person-days (antibiotic group). These results were different with reports from The Netherlands and the UK.^{19,23}

Anti epileptics was the lowest prescribed drugs among asthmatic and antibiotic patients. The incidences of antibiotic drug use in both groups were also low (0.002 cases/1000 person-days). These results were in line with report from The Netherlands (cumulative incidence of AEDs was 0.67 per 1000 children, and the prevalence 4.0 per 1000 children).⁹

B. The Incidence Risk Ratio

From table 2, the incidence risk ratio of anti psychotropic drug use was 1.21 (1.18-1.29). It means that the asthmatic patients are 1.21 times more likely than the antibiotic patients to receive psychotropic drugs over the 8 years period in this study. If we stratified the psychotropic drugs into the groups of psychotropic drugs (table 6), the highest incidence risk ratios belongs to anti psychotics (1.52). It means that the asthmatic patients are 1.52 times more likely than the antibiotic patients to receive anti psychotics over the 8 years period in this study. The anti epileptics and the anxiolytics have a similar incidence risk ratio (1.16 and 1.17) respectively. The similarities are less interesting than the fact that for some drugs the prevalence in prescription rates differed more than in others. The incidence risk ratio for centrally acting simpatomimetics and hypnotics/sedatives were quite similar (1.29 and 1.33) respectively. For anti depressants, the incidence risk ratio was less than 1 (0.82), it means that the antibiotic patients have a higher risk receiving anti depressants

over the 8 years period in this study compared to asthmatic patients.

These findings support other findings showing a higher incidence of psychiatric disorder in asthmatic children.^{3,8,11,13,14,16,21,22} In contrast with anti depressants, the incidence of receiving the anti depressants is higher in antibiotic group.

In table 3 and 4, we stratified anti depressants into two classes (non-selective monoamine reuptake inhibitors and selective serotonin reuptake inhibitors. In the index and reference group, selective serotonin reuptake inhibitors were the most frequent prescribed drugs (more than 50%), followed by non-selective monoamine reuptake inhibitors (more than 37%). This result has been confirmed by Mauro Percudani et.al, who found among 4252 patients received anti depressants, 2814 (66%) patients received one of the selective serotonin reuptake inhibitors.¹² In contrast with report from The UK, from 93,091 prescriptions of anti depressants, 55.7% were tricyclic antidepressants (TCAs) and 41.3% were selective serotonin reuptake inhibitors (SSRIs).

As can be seen in table 5, the incidence risk ratio for non-selective monoamine reuptake inhibitors is 0.88, showing the risk of receiving those drug group is higher in antibiotic patients during the study period. The most frequent drug in non-selective monoamine reuptake inhibitors is amytriptilin (IRR=0.87). The incidence risk ratio in selective serotonin reuptake inhibitors is 0.74 and the most frequent drug in this group is paroxetine. The frequent use of paroxetine was in line with Mauro Percudani report.¹²

In the group of stimulants, the most frequent prescribed drug was Methylphenidate (almost 100%). These results were in line with report from the Netherlands about increase use of psychotropic drugs.¹⁰ Asthmatic patients are 1.30 times more likely than the antibiotic patients to receive methylphenidate over the 8 years period in this study.

Conclusions

We found that the prevalence of asthma in male were larger than in female prior to 14 years. As children get older, the difference between the sexes narrows and by adulthood the prevalence of asthma is greater in women than in men.

Asthmatic patients received more often any psychotropic drugs compared to antibiotic patients except for anti depressants.

Stimulants were the most widely used psychotropic drugs after the initiation on asthma medication in children and adolescents in asthmatic and antibiotic groups over the eight years study (1999-2006).

Limitations And Suggestions

As in every study using prescription data, no diagnoses are included. We only see the drug prescription as a proxy, if the patients received two proxy drugs per year; we included them in our study population. We didn't see the interval between the first and the second prescription of the proxy drug. Another limitation is no DDD investigation, we only focus on the first anti psychotropic drug which prescribed after the index date/ matched date

It would be very interesting if we see the interval between the first and the second prescription of the proxy drug, and also if we investigate the severity of asthma using DDD before the patients receive psychotropic drugs. Another suggestion is to investigate psychotropic drugs use before the index date. For further research, the stratification by age and gender of incident users is also important

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