

Psychotropic Medication in Children: A Study From The Netherlands

Eric Schirm, MPharmSc*; Hilde Tobi, PhD*; Julie M. Zito, PhD‡; and
Lolkje T. W. de Jong-van den Berg, PhD*§

ABSTRACT. *Objective.* Although there is a global concern about the increased use of psychotropic agents in children, most research literature originates in the United States and is based on figures from the first half of the 1990s. Also, few studies document the use of various types of psychotropic agents. The objective of this study was to investigate the use of psychotropic medication in children in the Netherlands and to determine whether this corresponds with previously reported figures from the United States.

Methods. A drug utilization study based on computerized pharmacy dispensing records was conducted from 1995 to 1999 for children aged 0 to 19 years in the north of the Netherlands.

Results. Stimulants were the most widely used psychotropic agents among 0- to 19-year-olds (prevalence: 7.4/1000 in 1999), followed by hypnotics/anxiolytics (6.9/1000) and antidepressants (4.4/1000). Prevalence rates of stimulants increased from 1.5/1000 in 1995 to 7.4/1000 in 1999. Incidence rates, proportion of girls, and duration of stimulant treatment increased as well. Changes in prevalence rates of other psychotropic agents were much smaller than those of stimulants. Finally, the vast majority of children who were treated with psychotropic agents used only 1 agent at a time.

Conclusion. The prevalence of stimulant use in the Netherlands is much lower than reported previously (28/1000 children in 1995) from the United States, and differences also existed with regard to the use of other psychotropic agents and combinations of psychotropic agents. However, the increase in Dutch stimulant use agrees with the previously reported 2.5-fold increase in the United States and shows that the increased use of stimulants is not limited to the United States. *Pediatrics* 2001; 108(2). URL: <http://www.pediatrics.org/cgi/content/full/108/2/e25>; *child, pediatrics, psychotropic drugs, drug utilization study, pharmacoepidemiology.*

ABBREVIATIONS. ATC, Anatomic Therapeutic Chemical.

From the *Groningen Institute for Drug Exploration (GUIDE), University of Groningen, University Centre for Pharmacy, Section of Social Pharmacy and Pharmacoepidemiology, Groningen, The Netherlands; ‡University of Maryland, Baltimore, Maryland; and §InterAction Working Group, Northern Netherlands, The Netherlands.

Received for publication Jan 26, 2001; accepted Apr 2, 2001.

Reprint requests to (L.T.W.d.J.-v.d.B.) University Centre for Pharmacy, Section of Social Pharmacy and Pharmacoepidemiology, Antonius Deusinglaan 1, 9713 AV Groningen, The Netherlands. E-mail: l.t.w.dejong-van.den.berg@farm.rug.nl

PEDIATRICS (ISSN 0031 4005). Copyright © 2001 by the American Academy of Pediatrics.

There is a growing concern about the increasing number of children who use psychotropic medication. Major concerns involve the lack of evidence regarding safety and efficacy of the majority of psychotropic agents in children, in particular during long-term, and the possible overprescribing.^{1,2} The increased use of medication for attention-deficit/hyperactivity disorder has been well documented. In the United States, the number of children who receive stimulants increased approximately 2.5-fold in the first half of the 1990s.³ In 1995, approximately 2.8% of 5- to 18-year-old children in the United States and up to 1.2% of the 2- to 4-year-olds in the Midwestern Medicaid program were treated with stimulants.^{3,4} From 1992 to 1995, the absolute number of prescriptions for clonidine had increased approximately fivefold in the United States.⁵ Although there is a global concern about the increased use of psychotropic agents in children, most research literature originates from the United States and is based on figures from the first half of the 1990s. Also, few studies document the use of various types of psychotropic agents.^{2,4} Especially in view of the documented increases, it is important to investigate the use of all types of psychotropic agents and to assess whether the reported figures from the United States are representative of those in Europe. Here, we present recent prescribing figures from outside the United States, based on 1995 to 2000 computerized pharmacy data of the northern part of the Netherlands. The specific aim of this study was to investigate trends over time of the use of all types of psychotropic medication and to evaluate in more detail the use of stimulants.

METHODS

Population

In the Netherlands, people register with 1 pharmacy and obtain all of their medication from that pharmacy so that a complete medication history is available in the database. Previous studies demonstrated that dispensing data from Dutch pharmacies offers an accurate survey of the use of prescription drugs.^{6,7} Drugs used during hospital stay (inpatients) and over-the-counter medication are not included. This study was performed with pharmacy dispensing data from the InterAction database, which is part of the collaboration between community pharmacists in the northern part of the Netherlands and the University of Groningen. The InterAction database comprises all prescriptions of approximately 120 000 people from 1994 to mid-2000.^{8,9} Registration is irrespective of any health insurance (including people who are not insured) and thus is representative for the general population. From 1995 to 1999, all children aged 0 to 19 years on January 1 were

selected from the database. The total population estimates were based on general population statistics and the number of prescriptions for children in the database and ranged from 31 140 in 1995 to 37 670 in 1999.

Design

Psychotropic drugs were defined according to World Health Organization categories and comprised the following subgroups of the Anatomic Therapeutic Chemical (ATC) classification system¹⁰: stimulants (ATC group N06BA), antidepressants (ATC group N06A), antipsychotics (ATC group N05A excluding lithium), lithium (ATC group N05AN01), clonidine (ATC group N02CX02), and hypnotics/anxiolytics (ATC group N05B + N05C). Anticonvulsants were excluded because the main use of anticonvulsants in children is in the treatment of epilepsy. For the same reason, all prescriptions with rectal and intravenous dosage forms and all prescriptions for the benzodiazepines clobazam and nitrazepam were excluded.

The study consisted of 2 parts. In the first part of the study, we looked at the major types of psychotropic agents. Prevalence and incidence rates were determined per drug group and year and were defined as the number of youths who had received any prescription (prevalence rate) or the first prescription available in the database in case of incidence rates for the type of psychotropic per 1000 youths in the population. To determine incident use, we used the year before the study period (1994) as a washout period; therefore, incident users had not had any prescriptions for the particular psychotropic agent for at least 1 year. For both prevalence rates and incidence rates, a χ^2 test for trend was performed. The extent of monotherapy was expressed for 1999 per drug group as the percentage of children who used the particular psychotropic agent without psychotropic comedication.

The second part of the study focused on the use of stimulants. First, for the years 1995 to 1999, the prevalence rates were calculated as stratified by age group (0–4, 5–9, 10–14, and 15–19 years) and gender. Second, the duration of stimulant therapy was analyzed using the Kaplan-Meier estimator. Stimulant therapy was considered to have been stopped when a child had not used stimulants for at least 180 consecutive days. To compare the duration of stimulant therapy over time, we divided the population into 2 subgroups: children who started stimulant therapy between 1995 and mid-1997 ($n = 98$) and children who started between mid-1997 and 1999 ($n = 271$). In both groups, the follow-up window was 2.5 years. Because data were available through mid-2000, the 180-day criterion for stopping was used in both groups. A log-rank test was performed to investigate a difference in the duration of therapy. All statistical analyses were performed using SPSS (version 9.0; SPSS, Inc, Chicago, IL).

RESULTS

Table 1 shows the prevalence and incidence rates of all types of psychotropic agents for 0- to 19-year-olds from 1995 to 1999. Stimulants were used to the greatest extent (prevalence: 7.4/1000 in 1999), followed by hypnotics/anxiolytics (6.9/1000) and antidepressants (4.4/1000). Prevalence rates of stimulants increased from 1.5 per 1000 in 1995 to 7.4 per 1000 in 1999. Incidence rates increased significantly as well: from 1.0 per 1000 in 1995 to 3.4 per 1000 in 1999. Other smaller but statistically significant changes over time were the increased prevalence rates of antipsychotics and hypnotics/anxiolytics and the decreased incidence rates of clonidine use.

In the majority of cases, children received monotherapy (Table 2). Approximately 6% of the children who were treated with clonidine used a stimulant concurrently (data not shown).

Table 3 shows the use of stimulants in more detail. For all years, the highest prevalence rate by far is found in the age group of the 5- to 9-year-olds (13.9/1000 in 1999), followed by the age group of the 10- to 14-year-olds (10.0/1000 in 1999). In the total study period, far more boys than girls received stimulants, but the difference declined. In 1995, the overall gender ratio (M:F) for 0- to 19-year-olds who were receiving stimulant treatment was 8.4:1; in 1999, it was 5.5:1.

Figure 1 shows the duration of stimulant therapy for patients with a stimulant prescription between 1995 and mid-1997 (early group) or between mid-1997 and 1999 (late group). Half of the children had stopped medication within 9 months in the early group, whereas termination of drug therapy for half of the children of the late group did not occur for nearly 20 months. Comparison of treatment time in both groups showed a significant difference ($P = .03$).

TABLE 1. Use of Psychotropic Agents by Children 0 to 19 Years Old in the Northern Netherlands, 1995 to 1999

Agent	1995 (Rate* [n])	1996 (Rate* [n])	1997 (Rate* [n])	1998 (Rate* [n])	1999 (Rate* [n])
Stimulants					
Prevalence rate†	1.5 (47)	2.2 (76)	2.9 (105)	5.0 (185)	7.4 (278)
Incidence rate†	1.0 (31)	1.4 (47)	1.5 (53)	3.0 (109)	3.4 (129)
Antidepressants					
Prevalence rate	3.8 (117)	4.3 (148)	4.6 (166)	4.7 (172)	4.4 (166)
Incidence rate	2.8 (88)	2.8 (95)	3.1 (111)	3.2 (118)	2.8 (105)
Antipsychotics					
Prevalence rate†	1.6 (51)	2.8 (95)	2.4 (86)	3.1 (112)	3.4 (128)
Incidence rate	1.1 (35)	1.9 (66)	1.3 (46)	1.8 (67)	1.7 (63)
Lithium					
Prevalence rate	0.1 (3)	0.2 (6)	0.2 (7)	0.2 (6)	0.2 (6)
Incidence rate	0.1 (2)	0.1 (3)	0.1 (3)	0.1 (2)	0.1 (3)
Clonidine					
Prevalence rate	2.2 (69)	3.5 (121)	3.5 (126)	3.6 (132)	3.1 (116)
Incidence rate†	1.7 (54)	2.1 (71)	1.4 (51)	1.4 (52)	1.1 (42)
Hypnotics/anxiolytics					
Prevalence rate†	5.4 (167)	6.1 (209)	7.2 (261)	6.8 (251)	6.9 (259)
Incidence rate	4.6 (142)	5.3 (182)	6.0 (217)	5.3 (194)	5.1 (193)
Total study population	31 140	34 367	36 379	36 719	37 670

* Prevalence rates and incidence rates are expressed as number of children per 1000 children in the population.

† Significant trend at .05 level.

TABLE 2. Proportion of Children Using a Psychotropic Agent Without Psychotropic Comedication, Northern Netherlands, 1999

Drug Group	Monotherapy
Stimulants (<i>n</i> = 278)	89.6%
Antidepressants (<i>n</i> = 166)	84.3%
Antipsychotics (<i>n</i> = 129)	68.2%
Lithium (<i>n</i> = 6)	66.7%
Clonidine (<i>n</i> = 116)	86.2%
Hypnotics/anxiolytics (<i>n</i> = 259)	93.4%

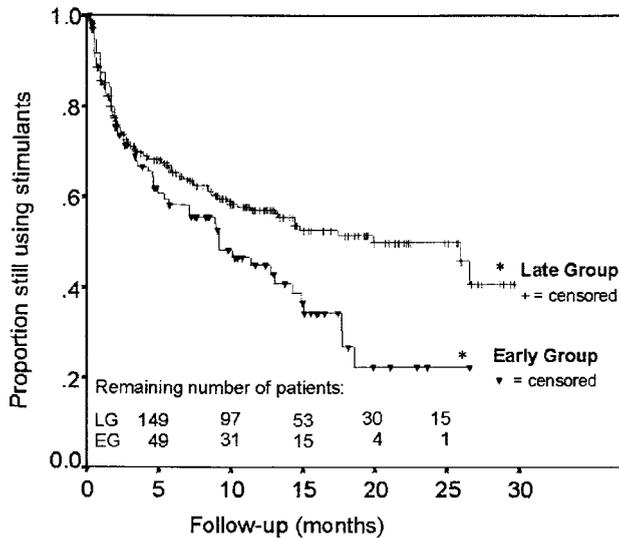


Fig 1. Kaplan-Meier curves for Dutch children who started stimulant therapy between 1995 and mid-1997 (*n* = 98) or between mid-1997 and 1999 (*n* = 271).

DISCUSSION

The main finding of this study is that the use of stimulants in the Netherlands is substantially lower than that in the United States (3.2/1000 5- to 9-year-olds in 1995 compared with 28/1000 5- to 18-year-olds in 1995 in the United States) but that the sharp increase in the use of stimulants is present in both countries.

Limitations

The database is not able to detect loss to follow-up (eg, by moving). This means that children who are lost to follow-up are still counted as part of the total

population. Although there is little mobility in the region of study, this might result in an underestimation of drug utilization. Another limitation of this study is that there are no data on diagnoses. Therefore, statements about the appropriateness of drug use cannot be made.

Prevalence and Trends Over Time

Our data show that stimulants were the most frequently prescribed psychotropic agents in 1999 (prevalence: 7.4/1000), followed by the hypnotics/anxiolytics (6.9/1000) and the antidepressants (4.4/1000). Although a comparison with use in the United States is difficult because of methodological reasons, it can be said generally that Jensen et al² found the prescribed number of stimulants in the United States to be at least twice as high as antidepressants and hypnotics/anxiolytics. By comparison, the present study showed stimulant and hypnotic/anxiolytic rates to be nearly comparable. For a good interpretation of the use of antidepressants, it should be kept in mind that antidepressants also are prescribed to children for nocturnal enuresis.

The difference in prevalence of stimulant use between our figures and figures from the United States is striking. In 1995, approximately 28/1000 of US 5- to 18-year-olds used stimulants.³ We found prevalence rates of 3.2/1000 for 5- to 9-year-olds and 1.3/1000 for 10- to 14-year-olds in 1995, which is approximately 10 times lower. Although we should keep in mind prevalence variations within the United States,^{11,12} our figures indicate that the use of stimulants clearly is lower than that reported from the United States. However, the increase in Dutch stimulant use agrees with the previously reported 2.5-fold increase in the United States³ and also has been documented in Australia (3.4-fold from 1988 to 1993)¹³ and Canada (4-fold from 1990 to 1995).¹⁴ This shows that the increased use of stimulants is not limited to the United States.

Combined Drug Therapy

Although not generally supported by safety and efficacy data, combined pharmacotherapy has become a frequent practice in child and adolescent psychiatry.^{15,16} In the United States, 49% of children

TABLE 3. Use of Stimulants by Age Group and Gender, Northern Netherlands, 1995 to 1999

Group	1995 (Rate* [n])	1996 (Rate* [n])	1997 (Rate* [n])	1998 (Rate* [n])	1999 (Rate* [n])
0- to 4-year-olds	1.0 (7)	0.9 (7)	0.7 (6)	0.8 (7)	2.3 (19)
Boys	1.9 (7)	1.7 (7)	1.5 (6)	1.4 (6)	4.0 (16)
Girls	0.0 (0)	0.0 (0)	0.0 (0)	0.2 (1)	0.7 (3)
5- to 9-year-olds	3.2 (27)	5.6 (49)	6.4 (60)	9.5 (92)	13.9 (136)
Boys	5.7 (24)	9.7 (43)	10.7 (50)	15.7 (77)	23.0 (116)
Girls	0.7 (3)	1.4 (6)	2.1 (10)	3.1 (15)	4.2 (20)
10- to 14-year-olds	1.3 (10)	1.9 (17)	3.0 (29)	7.4 (70)	10.0 (98)
Boys	2.0 (8)	3.1 (8)	5.1 (25)	12.8 (62)	16.4 (81)
Girls	0.5 (2)	0.7 (2)	0.9 (4)	1.8 (8)	3.5 (17)
15- to 19-year-olds	0.4 (3)	0.4 (3)	1.1 (10)	1.7 (16)	2.5 (25)
Boys	0.8 (3)	0.5 (1)	1.7 (8)	3.3 (15)	4.3 (22)
Girls	0.0 (0)	0.2 (0)	0.4 (2)	0.2 (1)	0.6 (3)
Estimated total population	31 140	34 367	36 379	36 719	37 670

* Prevalence rates are expressed as number of children with prescribed stimulant per 1000 in the population.

with attention-deficit/hyperactivity disorder received concomitant psychotropic treatment.¹⁷ Our study shows that in the majority of cases, Dutch children are treated with only 1 psychotropic agent at a time. So another interesting difference with treatment patterns in the United States relates to the use of monotherapy in the vast majority of psychotropic therapy for children in the Netherlands.

Increase of Stimulant Users

In explaining the increased use of psychotropic agents and of stimulants in particular, several factors have been suggested: a heightened awareness of psychiatric disorders in children, resulting in more children starting drug therapy; an increase of girls being treated; and an increased duration of drug treatment.^{3,18} Our findings of an increased number of children starting stimulant therapy and a decreased gender ratio support these explanations. Moreover, in this study, using a longitudinal model, we were able to follow individual stimulant-treated children and were able to confirm reported findings from cross-sectional studies pertaining to the increased duration of stimulant therapy.

CONCLUSION

The prevalence of stimulant use in the Netherlands is substantially lower than that in the United States. Differences also existed with regard to the use of other psychotropic agents and combinations of psychotropic agents. However, in both the Netherlands and the United States, the use of stimulants has increased. Prevalence variations may reflect regional variations in clinical practice styles.¹² Some have suggested a difference between British and American practices, and our findings indicate that this is the case for the Netherlands as well.^{19,20} The findings emphasize that data from 1 country are not sufficient to characterize current trends in the prescription of psychotropic drugs for children and adolescents.

ACKNOWLEDGMENTS

We thank Dr C. J. J. Ketelaars and Prof. R. B. Minderaa of the Department of Child and Adolescent Psychiatry, Academic Hospital Groningen, the Netherlands, for reviewing the manuscript.

REFERENCES

1. Angold A, Erkanli A, Egger HL, Costello EJ. Stimulant treatment for children: a community perspective. *J Am Acad Child Adolesc Psychiatry.* 2000;39:975–984
2. Jensen PS, Bhatara VS, Vitiello B, Hoagwood K, Feil M, Burke LB. Psychoactive medication prescribing practices for U. S. children: gaps between research and clinical practice. *J Am Acad Child Adolesc Psychiatry.* 1999;38:557–565
3. Safer DJ, Zito JM, Fine EM. Increased methylphenidate usage for attention deficit disorder in the 1990s. *Pediatrics.* 1996;98:1084–1088
4. Zito JM, Safer DJ, dosReis S, Gardner JF, Boles M, Lynch F. Trends in the prescribing of psychotropic medications to preschoolers. *JAMA.* 2000; 283:1025–1030
5. Swanson JM, Flockhart D, Udrea D, Cantwell D, Connor D, Williams L. Clonidine in the treatment of ADHD: questions about safety and efficacy. *J Child Adolesc Psychopharmacol.* 1995;5:301–304
6. De Jong-van den Berg LTW, Feenstra N, Toft Sorensen H, Cornel MC, EuroMAP Group. Improvement of drug exposure data in a registration of congenital anomalies. Pilot study: pharmacist and mother as sources for drug exposure data during pregnancy. *Teratology.* 1999;60:33–36
7. Lau HS, De Boer A, Beuning KS, Porsius A. Validation of pharmacy records in drug exposure assessment. *J Clin Epidemiol.* 1997;50:619–625
8. Tobi H, Van den Berg PB, De Jong-van den Berg LTW. The InterAction database: synergy of science and practice in pharmacy. In: Brause RW, Hanisch E, eds. *Medical Data Analysis. Lecture Notes in Computer Sciences* (1933). Frankfurt, Germany: Springer; 2000:206–211
9. Schirm E, Van den Berg PB, Gebben HJ, Sauer PJJ, De Jong-van den Berg LTW. Drug use of children in the community assessed through pharmacy dispensing data. *Br J Clin Pharmacol.* 2000;50:473–478
10. World Health Organization Collaborating Centre for Drug Statistic Methodology. *Guidelines for ATC Classification and DDD Assignment.* Oslo, Norway: World Health Organization; 1999
11. Rappley MD, Gardiner JC, Jetton JR, Houang RT. The use of methylphenidate in Michigan. *Arch Pediatr Adolesc Med.* 1995;149:657–679
12. Zito JM, Safer DJ, Riddle MA, Johnson RE, Speedie SM, Fox M. Prevalence variations in psychotropic treatment of children. *J Child Adolesc Psychopharmacol.* 1998;8:99–105
13. Valentine J, Zubrick S, Sly P. National trends in the use of stimulant medication for attention deficit hyperactivity disorder. *J Pediatr Child Health.* 1995;32:223–227
14. Hollander E, Quinn D, Hunt RD, Perry PJ. The ADHD debate: stimulants or alternative agents. *Primary Psychiatry.* 1996;3:52–55
15. Wilens TE, Spencer T, Biederman J, Wozniak J, Connor D. Combined pharmacotherapy: an emerging trend in pediatric psychopharmacology. *J Am Acad Child Adolesc Psychiatry.* 1995;34:110–112
16. Woolston JL. Combined pharmacotherapy: pitfalls of treatment. *J Am Acad Child Adolesc Psychiatry.* 1999;38:1455–1457
17. Zarin DA, Suarez AP, Pincus HA, Kupersanin E, Zito JM. Clinical and treatment characteristics of children with attention-deficit/hyperactivity disorder in psychiatric practice. *J Am Acad Child Adolesc Psychiatry.* 1998;37:1262–1270
18. Swanson JM, Lerner M, Williams L. More frequent diagnosis of attention deficit-hyperactivity disorder. *N Engl J Med.* 1995;333:944
19. Bramble D. Prescribing practices in Britain. *J Am Acad Child Adolesc Psychiatry.* 1995;34:1–2
20. Romano G. The TEN interview: Sir Michael Rutter. *Econ Neurosci.* 2000;2:31–33

Psychotropic Medication in Children: A Study From The Netherlands
Eric Schirm, Hilde Tobi, Julie M. Zito and Lolkje T. W. de Jong-van den Berg
Pediatrics 2001;108;e25
DOI: 10.1542/peds.108.2.e25

Updated Information & Services

including high resolution figures, can be found at:
<http://pediatrics.aappublications.org/content/108/2/e25>

References

This article cites 18 articles, 1 of which you can access for free at:
<http://pediatrics.aappublications.org/content/108/2/e25.full#ref-list-1>

Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):
Pharmacology
http://classic.pediatrics.aappublications.org/cgi/collection/pharmacology_sub

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
<https://shop.aap.org/licensing-permissions/>

Reprints

Information about ordering reprints can be found online:
<http://classic.pediatrics.aappublications.org/content/reprints>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since . Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2001 by the American Academy of Pediatrics. All rights reserved. Print ISSN:

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Psychotropic Medication in Children: A Study From The Netherlands
Eric Schirm, Hilde Tobi, Julie M. Zito and Lolkje T. W. de Jong-van den Berg
Pediatrics 2001;108:e25
DOI: 10.1542/peds.108.2.e25

The online version of this article, along with updated information and services, is
located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/108/2/e25>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since . Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2001 by the American Academy of Pediatrics. All rights reserved. Print ISSN:

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

