Stimulant medication use among Flemish students: results from an exploring secondary data analysis 1965-2005

by

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Abstract

Background/Aim

Recent media coverage in the Flemish media in Belgium reinforced the general public opinion on medication use among students, suggesting an alarming magnitude and a rising trend, with the use of stimulants as a specific element for enhancing study performances. These assumptions needed scientific verification, which we intended to do with this study.

Method

Secondary data analysis was conducted on four Belgian studies on medication use among students from 1965, 1969, 1993 and 2005. The 2005 survey data are also used to give an insight in prevalence and frequency of use during exams and in other periods and to widen the scope to poly-substance use.

Main Findings

All studies show prevalence figures for stimulant medication use under 10%. Prevalence and frequency of use is highest during exam periods. No gender differences were found for stimulant medication use. Living status on the other hand is an influential factor: students living away from the parental home report higher prevalence rates than students still living in their parents' house. Prescription regulations seem to have a declining impact on the most popular products.

Conclusions/Discussion

Students' medication use, more particularly during exam periods, appears to be an all-time reality in Flanders. No indications for a rising trend were found. Although the extent of stimulant medication use is relatively limited, a small minority shows more risky consumption patterns: daily use of stimulant medication (incl. risky side effects) during exam periods and higher prevalence of poly-substance use. More research is needed, particularly on the most consumed products (e.g. methylphenidates) and on the supplying sources of this medication.

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Keywords

Students, substance abuse, central stimulants, residence characteristics, gender

Introduction

In the public opinion, one of the dominant ideas on the life-style of students is the prevailing medication use during exam periods. In December 2007 several journal articles in the Flemish part of Belgium reinforced this idea by reporting on a so-called alarming extent of medication use among students: according to a study of the health insurance company CM, eight out of ten Flemish students used medication during exam periods. This result was interpreted as an alarming new fact. Above all, it was an overreaction due to the misinterpretation by the media. By checking the original results it appeared that eight out of ten students did not use stress-coping or performance-enhancing medication in times of exams. Moreover, students' medication use was primarily characterised by the use of pain medication and herbal or dietary supplements (preparations of vitamins and/or minerals). This was also shown by other, international studies. 70.6% of U.S. college students reported last-week use of herbal and dietary supplements. No gender or age differences were reported. Vitamins and minerals were used by 59.7% of the students. Herbal products, like ginkgo biloba, St. John's wort, kava and valerian, were used by 31.3%. The use of these over-the-counter supplements was linked to distress and mental state problems, most particularly sleeping problems, anxiety and mood fluctuations (1).

In the prevalence figures of the CM study, sedative medication (7.7%) and stimulating medication (3.1%) were only reported occasionally during exam periods. These CM figures correspond more or less to those of a representative sample of students of the Association of University and Colleges Antwerp: 3.5% reported the use of sedative medication during exam periods, 2.6% reported the use of stimulant medication in exam period (2). But the media coverage put the public focus on the so-called growing medication use among students. The key question is if there really is an evolution towards a higher medication use among Flemish students. The aim of this study is to verify this assumed evolution for psychoactive stimulant medication, based on available research data in Belgium from 1965 onwards.

Medication use among students is often associated with negative emotions due to exam pressure. Emotions like anxiety, anger and depression increase during the week before the exams, compared to a typical week (3). To cope with these emotions and to perform better in studying, some students put their hopes in the non-medical use of stimulants. Insomnia, stress and anxiety were the most commonly mentioned reasons for taking non-prescribed benzodiazepines. Insomnia and stress were more mentioned by students with multiple social roles (professional occupation, parent), whereas anxiety was more mentioned by students without multiple social roles (4).

Most conducted studies on prescribed medication use among students indicate prevalence figures of less than 10%. In a large-scale Portuguese survey, 7.9% of undergraduate stu-

dents reported consumption of psychoactive medication (mostly psycholeptics and psychoanaleptics) in the previous fortnight. 7.2% used tranquilizers (anxiolytics, hypnotics and sedatives), 1.9% consumed psychoactive stimulants and 1.7% took antidepressants (5). An American survey showed that 5.4% of undergraduate students indicated non-medical use of stimulant medication, 2.9% sedative/anxiety medication and 2.0% sleeping medication during the past year (6). A recent study, based on the results of large-scale nationwide surveys, examined prevalence trends in non-medical use of prescription drugs among US college students (i.e. amphetamines, opioids, sedatives, tranquilizers). Results showed a steady increase in prevalence of life-time and last-year prevalence. The estimated last-year prevalence increased from 4.4% in 1993 to 10.0% in 2001 (7).

Regarding the non-medical use of stimulant medication among students, methylphenidate is a popular product overseas. Svetlov et al. state that in the United States methylphenidate is commonly used by college students for the preparation of exams, helping to enhance their concentration and study performance (8). This product is worldwide mostly sold under the brand name Ritalin®, in Belgium its brand name is Rilatine®. But there are also other stimulants for ADHD symptoms that are used as performance-enhancing agent, like the (dextro)amphetamines Aderall® and Dexedrine® (9). To students, there are even differences in motives to use one stimulant or the other. The work- or study-enhancing expectancies are higher for the non-medical use of Concerta®, a timed-release form of methylphenidate, whereas Ritalin® is more often non-medically used for partying (10).

The statement of widely used stimulants needs to be put in perspective. Most recent studies indicate a prevalence of 5.3% to 6.9% for non-medical methylphenidate use (9, 10, 11). Even if these seem rather low percentages, they represent a large part of the student population in real numbers. In the Antwerp student survey 1.5% of the student population, representing about 400 students on a total population of about 27,000, used stimulant medication on a daily basis during exam periods (2).

An important consideration is that the use of stimulant medication often appears to be illicit. Self-medication of stimulants seems to be even more in existence than the use of prescription stimulants. An American study indicated that the number of undergraduate students who reported illicit use of prescription stimulants exceeded the number of students who reported medical use of prescription stimulants for ADHD. The most cited sources of prescription stimulants for illicit use were friends and peers (12).

These results suggest that the overall use of stimulant medication is rather limited. Clear trends have not been detected in the literature. ADHD medication use seems to be quite popular in American student milieus, but is this just an overseas phenomenon or is it also a prevailing trend in Belgium? Our study aims at assessing the magnitude of and occurring trends in stimulant medication use among Flemish students, by comparing prevalence figures from studies. The influence of gender and residence status is also assessed.

Methods

This retrospective study of medication use among Flemish students over the last four decades is based on scarce data sources that are available. We conducted a literature study, searching the university library databases and Belgian medical journals for "students", "college", "stimulant", "medication" and "drug use". We managed to collect six relevant scientific studies on this subject:

- a survey on the use of stimulants, sleeping medication and sedatives during exam periods among students in Ghent in 1965 (13)
- a survey on the use of psychotropics among students in Leuven in 1967-1968 (14)
- a survey on the complaints of students in Ghent during exam periods in 1978 (15)
- a survey on the influence of exams on daily life habits of students in Leuven in 1980
 (16)
- a survey on substance use of students in Leuven in 1993 (17)
- a survey on substance use of students in Antwerp in 2005 (2).

Unfortunately, the 1978 and 1980 studies did not put a clear focus on medication use of students. Because of the limited data and vague description of methodology in both studies we decided not to include these in the data comparison.

To maximise the comparability of the data, we only took a look at common variables in the four remaining studies. First, we planned to take the results of both the use of stimulant medication and the use of sleeping medication or tranquilizers. But due to the incomparability of methods and/or results, we had to exclude the use of sleeping medication or tranquilizers from our study.

We took a look at the prevalence figures of stimulant medication use in the four selected studies. Where possible, gender and living status were added. Additionally, we included some other relevant results from the 2005 survey in Antwerp.

The 1965 study was a survey among students of the University of Ghent. A non-representative sample of 1,848 students completed a self-report questionnaire on substance use (83.7% male). Medication use was one of the topics and was divided into two main categories: stimulant medication and sleeping medication or tranquilizers. The pre-exam and exam period were indicated as reference periods for indicating the prevalence of medication use. Stimulant medication was subdivided into three categories. For our study we included the category "psychotonics", medication with a stimulant effect similar to amphetamines but with a different chemical structure, e.g. methylphenidate. The categories left out for comparison were "wekamines" (amphetamine-based products) and "strengthening products" (herbal or dietary supplements). The first category was left out because these products were withdrawn from the Belgian pharmacological market soon after the first studies. The second category was left out because our study does not include over-the-counter-supplements.

The 1968 study consisted of a survey among students of the University of Leuven. A nonrepresentative sample of 6,982 students completed a self-report questionnaire on substance use (77.1% male). Medication use was the central topic. The prevalence of medication use was based on last-year use. Two main categories were included: psychoanaleptics and psycholeptics. Since we only include stimulant medication in this article, the category psycholeptics was excluded. In the psychoanaleptics, we focus on the prescription stimulants.

The 1993 study was a survey among students of the University and Colleges in Leuven. A non-representative sample of 1,992 students completed a self-report questionnaire on substance use (50.9% male). Pre-exam period and exam period were the reference periods for indicating the prevalence of substance use. Medication use was one of the substance use topics and was then divided into six main categories. In this study, we only included the medication category "stimulants". Vitamins and tonics were excluded.

The 2005 study was a survey on substance use among students of the Antwerp University Association. A representative sample of 1,501 students was selected (46.9% male). Lastyear use as well as use during the three main periods (academic year, exam periods, holiday periods) served as reference periods for indicating prevalence and frequency of substance use. Medication use was one of the substance use topics, subdivided into three categories. For this study, only the category "stimulant medication" was included. In the questionnaire it was specified that over-the-counter products (homeopathic products, herbal or dietary supplements) were not considered stimulant medication.

All included studies made comparisons between two subgroups of students: residential students and commuter students. Residential students are students who live in a residence in the university city or surroundings, away from the parental home, during the week. Commuter students still live in the parental residence and shuttle between home and university/college.

Results

Psychoactive stimulant use over a period of 40 years

Table 1 shows the prevalence of psychoactive stimulant medication. Every reference period in the different studies indicates a prevalence level lower than 10%. At the end of the sixties the prevalence rate was just above 5%. The 2005 study shows a prevalence rate that is even below 3%. The 1993 study indicates higher prevalence figures: In the pre-exams the prevalence rate lies between the level of the preceding and following studies, but the prevalence in the exam period is clearly higher and approximates 10%.

The 1965 study measured the prevalence during exam periods, whereas the 1967-1968 study indicates the prevalence for last year use. Yet both studies show the same level of prevalence: 5.7%. Based on the results of the 2005 study, where both figures are almost as

high, it seems assumable that the level of stimulant medication use during exam period is a good indicator for the level of last year use.

No gender differences are found in three of the four studies. Only the most recent study showed significance in the higher prevalence rate among male students, compared to female students. On the other hand, living status is an overall influencing factor. In all four studies the prevalence of psychoactive medication use is higher among residential students, compared to commuter students living at home. The differences are the highest in the 1993 study.

Study	Prové &	Van de Voor-	Waege et al.	Waege et al.	Rosiers &	Rosiers &
	Varenne	de et al.	(1993)	(1993)	Van Hal	Van Hal
	(1965)	(1967-1968)			(2005)	(2005)
Number of re-	(n=1,848)	(n=6,982)	(n=1,936)	(n=2,007)	(n=1,501)	(n=1,501)
spondents						
Male/Female	M: 83.7%	M: 77.1%	M: 50.9% / F: 49,1%		M: 46.9% / F: 53.1%	
	F: 16.3%	F: 22.9%				
Residential/	R: 46.3%	R: 81.4%	R: 81.6%		R: 29.0% / C: 71.0%	
commuter	C: 53.7%	C: 18.6%	C: 18.4%			
Reference period	Exams	Last year	Exams	Pre-exams	Exams	Last year
Prevalence (%)	5.7%	5.7%	9.5%	3.6%	2.6%	2.9%
Numbers of	(n=106)	(n=395)	(n=183)	(n=73)	(n=39)	(n=44)
stimulant users						
Gender:	ns	ns	ns	-	-	**
Male (%)	5.4%	5.9%	8.9%			4.3%
Female (%)	7.6%	4.7%	10.4%			1.8%
Level of	p=0.12	p=0.07	p=0.27	-	-	p=0.004
significance						
Living status:	**	*	***	-	-	*
Residential (%)	7.6%	6.0%	13.2%			4.7%
Commuter (%)	4.1%	4.3%	5.6%			2.4%
Level of signifi-	p=0.001	p=0.04	p<0.001	-	-	p=0.04

Catovit®(80%)

Captagon® (14%)

Table 1: Prevalence of stimulant use among Flemish students 1965-2005

Most popular

cance

Rilatine®

(38.7%)

Rilatine®

(35.4%)

In both studies at the end of the sixties, Rilatine® is by far the most consumed stimulant medication. The 1993 study indicates the popularity of the brands Catovit® and Captagon®. The 1993 study did not mention Rilatine® anymore. Unfortunately, the 2005 study did not ask the respondents for the brands or products used. The overseas observed high level of Ritalin® use among students has not yet been reported in Belgium, partly because of lack of information. It could be that the recent rise of Rilatine® use in the general population leads to a higher degree of Rilatine® use among students. In the two last decades Rilatine® became popular again, as a prescription medication for ADHD symptoms (Figure 1).

products *** p<0.001

^{**} p<0.01

[°] p<0.05

ns not significant (p≥0.05)

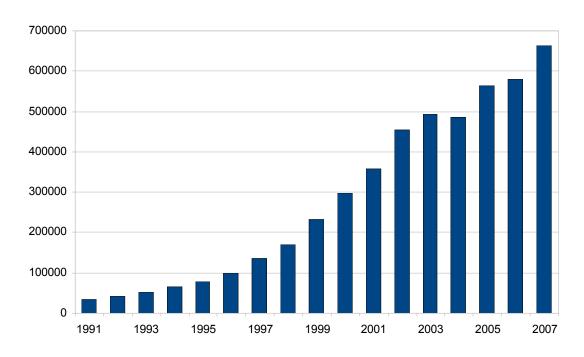


Figure 1: Sales evolution of Rilatine® packs in Belgium 1991-2007 (Source: IMS Health)

Other aspects of stimulant medication use: period and poly use

Table 2 shows the prevalence and frequency of stimulant use among last-year users in the 2005 study. Whereas in holiday periods (11.6%) and during the academic year (20.9%) only a minority of last-year users take this medication, almost every last-year user uses stimulants during exam periods. This supports the assumption that the prevalence in exam periods is a good indicator for last-year prevalence.

Daily use No use ≤ 1x/month 2-3x/month 1x/week 2-6x/week Academic year 79.1% 7.0% 2.3% 0.0% 4.7% 7.0% 7.0% Exam periods 9.3% 4.7% 4.7% 23.3% 51.2% 4.7% 4.7% 0.0% 88.4% 0.0% 2.3% Holiday periods

Table 2: Frequency of stimulant use in three periods (only last-year users) - 2005

Source: Rosiers & Van Hal (2007)

Regarding the frequency of stimulant medication use, only a small minority of the last-year users reports frequent use (≥ 1x/week) in academic year and holiday periods. This clearly differs from the exam periods. More than 3/4th of the last-year users indicate frequent stimulant medication use during exams. Half of last-year users even report daily use of these products. Extrapolated to the whole student population of 27,000 students, about 400 Antwerp students use stimulant medication on a daily basis during exam periods.

The results of the Antwerp survey also give some indications for poly-substance use among last-year users of stimulant medication. There are significant correlations between last-year

stimulant medication use and last-year use of beer ($\chi^2(1)=4.19$; p=0.04) and between last-year stimulant medication use and last-year use of cannabis ($\chi^2(1)=7.00$; p<0.01).

Conclusions and discussion

The results of this study show that there is no evidence to perceive/suggest that the stimulant medication use among students is dramatically high or booming. With prevalence rates constantly below 10%, even in exam periods, there is no evidence to reflect on the extent of students' psychoactive medication use as a worrying situation. The Flemish prevalence figures correspond to the international study results (5, 7).

Nevertheless, attention has to be paid to a minority of frequent users. As the results of the 2005 survey show, a small minority uses stimulant medication on a daily basis during exam periods. Nonmedical use of stimulants like methylphenidates incorporates potential risks, like cardiovascular problems, insomnia and gastro-intestinal discomfort (18). In 2007, the Food and Drug Administration in the USA directed manufacturers of ADHD stimulants to alert patients to possible cardiovascular risks and risks of adverse psychiatric symptoms associated with these medicines (19). In March 2008, the Belgian Centre for Pharmaco-therapeutic Information (BCFI) adopted the scientific statement of the American Heart Association Council on its website, pointing out the need for cardiovascular monitoring of children and adolescents before starting a stimulant medication treatment for ADHD (20, 21).

But there is more than the risk for side-effects of the use of stimulants. Nonmedical users of prescription stimulants are more likely to report poly-drug use and drug-related problems (11). This is confirmed by the 2005 survey results on poly-use in this study. According to McCabe & Boyd nonmedical users of psychoactive medication who obtain their medication from peers are more likely to report more frequent alcohol and drug use and a higher occurrence of heavy episodic drinking and problematic alcohol use (6).

The assumed trend of rising stimulant use is not found by comparing the four included studies. The 2005 prevalence figure is lower than those in the two studies of the late sixties. The 1993 study indicates higher prevalence rates, due to the popularity of Catovit®, a product with a so-called mild effect. Although Catovit® was perceived as a rather mild stimulant (prolintane + vitamins), it was withdrawn from the Belgian market in 1993 because the dangerous side effects like cardiovascular problems and anorexia were assessed to be more important than the therapeutic value of the product.

The results of our retrospective comparative study also indicate the popularity of Ritalin® / Rilatine® in the late sixties. But the 1993 study does not mention this brand anymore. This most certainly is a consequence of the fact that the delivering of Rilatine® was put under a more severe prescription regulation in 1969: the classification "narcotic substance" ("verdovingsmiddel" or "stupéfiant") was added in the product regulation, leading to a more tightened governmental control over pharmacy sales. But recent trends of increasing methylphenidate use among students in the U.S. could also move to Europe.

No gender differences were found in the four included studies. Concerning living status, significant differences were found between residential and commuter students. Students living in a residence away from home report higher prevalence of stimulant medication use, compared to students still living in the parental home. This finding corresponds to international findings. McCabe et al. reported that commuter status appears to have an impact on the prevalence of nonmedical use of prescription drugs, with higher rates in non-commuter colleges, compared to commuter colleges (7).

The lesser degree of parental monitoring among residential students could be an influencing factor. This was hypothesised as determinant for the higher consumption of tobacco, alcohol and recreative drugs (cannabis, cocaine, ecstasy and amphetamines) among residential students (22), but this hypothesis may be extended to stimulant medication use. Other studies indicate the manifest role of peers, mostly friends, in supplying (stimulant) medication to students (5, 6).

This study highlights the need for further research in this domain, with an additional focus on the use of psycholeptics. Most studies on medication use among students indicate higher prevalence rates for psycholeptics, compared to those for psychoanaleptics (4, 5, 23, 24).

Besides the enlarging of the scope, a more in-depth research approach of medication use among students is expedient. The sources of medication supply, the use of stimulant medication as a party drug and the reasons for using these stimulants could be important issues. Differences between commuter and residential students could be further explored, as well as other potential relevant characteristics, like the study discipline. Results of a French study indicate that medical students using psychoactive medication are more likely to experience feelings of anger, frustrations and bitterness, whereas psychology students using psychoactive medication are more likely to be susceptible to stress and to panic when they are in problematic situations (25).

References

- 1. Stasio MJ, Curry K, Sutton-Skinner KM, Glassman DM. Over-the-counter medication and herbal or dietary supplement use in college: dose frequency and relationship to self-reported distress. J Am Coll Health Assoc 2008;56:535-47
- 2. Rosiers J, Van Hal G. Bevraging van de AUHA-studenten over hun middelengebruik en daarmee verwante aspecten: de onderzoeksresultaten. In: Van Hal G, Rosiers J, Bernaert I, Hoeck S. In hogere sferen? Een onderzoek naar het middelengebruik bij Antwerpse studenten. Antwerpen: Universiteit Antwerpen; 2007. p.27-107 [in Dutch]
- 3. Noel NE, Cohen DJ. Changes in substance use during times of stress: college students the week before exams. J Drug Educ. 1997;27:363-72
- 4. Paredes NP, Miasso AI, Tirapelli CR. Consumption of benzodiazepines without prescription among firstyear nursing students at the university of Guayaquil, school of nursing, Ecuador. Rev Lat Am Enfermagem. 2008;16(especial):634-9
- 5. Cabrita J et al. Patterns and determinants of psychoactive drug use in Lisbon University students a population-based study. Pharm World Sci. 2004;26:79-82
- 6. McCabe SE, Boyd CJ. Sources of prescription drugs for illicit use. Addict Behav. 2005;30:1342-1350.

- McCabe SE, West BT, Wechsler H. Trends and college-level characteristics associated with the nonmedical use of prescription drugs among US college students from 1993 to 2001. Addiction. 2007;102:455-65
- 8. Svetlov SI, Kobeissy FH, Gold MS. Performance enhancing, non-prescription use of Ritalin: a comparison with amphetamines and cocaine. J Addict Dis 2007;26:1-6
- 9. McCabe SE, Knight JR, Teter JC, Wechsler H. Non-medical use of prescription stimulants among US college students: prevalence and correlates from a national survey. Addiction. 2005;99:96-106
- 10. DuPont RL, Coleman JJ, Bucher RH, Wilford BB. Characteristics and motives of college students who engage in nonmedical use of methylphenidate. Am J Addict. 2008;17:161-71
- McCabe SE, Teter CJ. Drug use related problems among nonmedical users of prescription stimulants: a web-based survey of college students from a Midwestern university. Drug Alcohol Depend. 2007;91:69-76
- 12. McCabe SE, Teter CJ, Boyd CJ. Medical use, illicit use and diversion of prescription stimulant medication. J Psychoactive Drugs. 2006;38:43-56
- 13. Prové W, Varenne G. Het gebruik van opwek-, slaap- en kalmeermiddelen door de studenten tijdens de blok- en examenperiode. Gent: Centrum voor Studie, Behandeling en Preventie van Alcoholisme en Toxicomanieën; 1965 [in Dutch]
- 14. Van de Voorde H, De Wijs-Koppen, O, Van Kerckvoorde J. Studenten en psychofarmaca. Leuven: K.U. Leuven; 1969 [in Dutch]
- 15. Hendrickx A, Bruyninckx R. Klachten van studenten in blok- en examenperiode aan de Rijksuniversiteit Gent. Resultaten van een studentenenquête. Belgisch Archief van Sociale Geneeskunde, Hygiëne, Arbeidsgeneeskunde en Gerechtelijke Geneeskunde. 1979;37:93-117 [in Dutch]
- 16. Bracke M, De Witte E. Onderzoek naar de invloed van de eksamens op enkele leefgewoonten bij de derdejaarsstudenten aan de Katholieke Universiteit Leuven. Farm Tijdschr Belg. 1980;5:283-8 [in Dutch]
- 17. Waege H, Bracke M, Degroote A, Hoornaert H. Genees- en genotsmiddelen bij de Leuvense studenten. Rapport studentenvoorzieningen nr. 6. Leuven: K.U. Leuven; 1994 [in Dutch]
- 18. Rosiers J. Dossier ADHD en middelengebruik. Brussel: VAD; 2004 [in Dutch]
- Food and Drug Administration (FDA). FDA directs ADHD drug manufacturers to notify patients about cardiovascular adverse effects and psychiatric adverse events, FDA News, Doc n° P07-26. 2007. Available from www.fda.gov/bbs/topics/NEWS/2007/NEW01568.html
- 20. Belgisch Centrum voor Farmacotherapeutische Informatie (BCFI). Aanbevelingen van de American Heart Association rond cardiovasculaire monitoring van kinderen en adolescenten vooraleer behandeling met centrale stimulantia in het kader van ADHD te starten. Available from www.bcfi.be/nieuws/index.cfm?welk=268&keyword=american%20heart%20association&thisYear=2008 [In Dutch]
- 21. Vetter VL, Elia J, Erickson C, Berger S, Blum N, Uzark K, Webb, CL. Cardiovascular monitoring of children and adolescents with heart disease receiving stimulant drugs. A scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing. Circulation. 2008;117:2407-23
- 22. Van Hal G, Boot C, Rosiers J, Meijman FJ. Genotmiddelengebruik bij kot- en thuisstudenten in Antwerpen en Amsterdam: is een gedifferentieerde preventieve aanpak vereist? Tijdschrift voor Onderwijsrecht en Onderwijsbeleid, in press [in Dutch]
- 23. Henriquez PC, de Carvalho AMP. Perceptions of drugs benefits and barriers to quit by undergraduate health students. Rev Lat Am Enfermagem. 2008;16(especial): 621-6
- 24. McCabe SE. Correlates of nonmedical use of prescription benzodiazepine anxiolytics: results from a national survey of U.S. college students. Drug Alcohol Depend. 2005;79:53-62
- 25. Baumann M, Spitz E. Advising adolescents on the use of psychotropic medication: attitudes among medical and psychology students. Subst Abuse Treat Prev Policy. 2007;12:21