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Usage of antifungal drugs for therapy of genital *Candida* infections, purchased as over-the-counter products or by prescription: I. Analyses of a unique database

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Objectives: To present sales figures of antifungal drugs for treatment of genital *Candida* infections in females, which had been purchased in the Swedish county of Skåne (with approximately 1.2 million inhabitants) during the 1990s. To study the relative proportions of the drugs sold by prescription and as over-the-counter (OTC) products.

Methods: Sales figures of antifungal drugs for therapy of vulvovaginal candidiasis (VVC) and such recurrent infections (RVVC), for the years 1990–99, were collected from the 'ACS' database of the National Corporation of Swedish Pharmacies.

Results: The study showed an increase in sales of the type of drugs studied from 45 000 packages in 1990 until mid-93/94, when approximately 70 000 packages were sold (mainly azoles for topical use and fluconazole for oral intake). Thereafter there was a decrease until the end of November 1999, when 54 000 packages were purchased. Of the total sales, 93% were OTC products. Sales of clotrimazole and econazole (for vaginal installation) in 1993–1994 were equal to 85–90 packages/1000 women in the age group 15–45 years. Extremely high sales volumes of fluconazole and itraconazole, for one single year each, could be explained by marketing-related activities directed to the medical community.

Conclusions: As many women with RVVC are not cured by iatrogenic initiatives and women consider themselves able to diagnose episodes of genital *Candida* infection, affected women generally turn to self-medication with antifungal OTC products. This stresses the role of pharmacy counseling. Short-term marked alterations in sales volumes may be due to marketing factors rather than changes in the epidemiology of genital *Candida* infections.

Key words: ANTIFUNGAL DRUGS; VULVOVAGINAL CANDIDIASIS; RECURRENT VULVOVAGINAL CANDIDIASIS; PRESCRIPTIONS; OVER-THE-COUNTER PRODUCTS

It is estimated that approximately three-quarters of all women will suffer from at least one episode of vulvovaginal candidiasis (VVC) during their lifetime and that about 5% will experience recurrent episodes (RVVC)^{1,2}. However, the

proportion of false diagnoses of attacks of RVVC is high³. Not only the women themselves with an assumed history of RVVC and with current symptoms generally associated with VVC, but also health-care providers overdiagnose the pre-

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sence of yeast fungi in the genital tract in up to half of all such instances⁴.

Women with RVVC may have consulted one or more physician(s) several times before continuing self-treatment with antifungal drugs available as over-the-counter (OTC) products, or they even start such treatment directly after counseling with a pharmacist^{5,6}. Thus, hospital and outpatient clinic records can hardly serve as reliable sources of information in attempts to understand the epidemiology of genital *Candida* infections.

The majority of strains causing both VVC and RVVC belong to *C. albicans*. A switch of flora to non-*albicans* strains – with a natural low susceptibility to azole drugs – may, however, occur in RVVC cases, which may result in therapeutic problems^{7,8}.

All pharmacies in Sweden are state-owned and the only ones that are allowed to sell medical drugs in the country, including antifungal OTC products. The sales of all medical drugs are registered in a database⁹, which offers a unique opportunity to study usage not only of prescribed drugs, but also of OTC products.

The present study was undertaken to analyze the sales figures of antifungal drugs, both prescriptions and OTC products, aimed at the therapy of VVC/RVVC, which had been purchased at pharmacies in Skåne county, Sweden, during the 1990s.

MATERIAL AND METHODS

Study population

The female population of Skåne county during the 1990s consisted of approximately 660 000 individuals.

Antifungal drugs available during the study period

The drugs for therapy of VVC/RVVC that were available in Sweden during the 1990s, as well as their trade names, galenic forms, available package sizes, year of registration in Sweden and from which year they were available as OTC products, are shown in Table 1.

Database and analyses performed

Data on drugs sold more or less exclusively for therapy of genital *Candida* infections in females were studied. The data were derived from Apoteket AB's database 'ACS' for the period January 1990 to the end of November 1999⁹. At the start of collection of the 'ACS' data in 1974, it surveyed one in 288 prescriptions. Later, this was the case for one in every 25 samples. From 1997 onwards, the database has registered all dispensed prescriptions. The data recorded for prescriptions are: trade name, total cost and quantity of the drugs purchased, and sex and year of birth of the customer. Also, the sum paid by the customer, if any (related to subsidies), is registered. All OTC sales are also registered, but could not be analyzed as to sex and age of consumer, as customers are not requested to supply any personal information.

We analyzed all packages of antifungal drugs aimed for vaginal installation, i.e. clotrimazole (Canesten[®]), econazole (Pevaryl[®]) and miconazole (Daktar[®]). Furthermore, we analyzed figures for one capsule of 150 mg fluconazole (Diflucan[®]) and four capsules of 100 mg itraconazole (Sporanox[®]) (which package sizes are more or less only used for therapy of VVC/RVVC). We chose to analyze the number of packages sold, instead of Defined Daily Dose, which we found more relevant for sales of drugs particularly used to treat VVC and RVVC. For fluconazole and itraconazole, we investigated only the sales figures for the above-mentioned package sizes, because they are especially aimed for these two indications.

The number of pharmacies in Skåne remained fairly constant, at around 100, during the study period. Pharmacies in the county had shelves displaying OTC medications for self-selection of available products by the customers themselves.

RESULTS

Figure 1 shows the total consumption of vaginal preparations of econazole, miconazole and clotrimazole during the period January 1990–November 1999. Usage of these drugs increased from approximately 45 000 packages in 1990 to approximately 70 000 in 1994, an increase of 38%.

Table 1 Drugs available for therapy of vaginal *Candida* infections in Sweden during the 1990s

Substance name	Preparation	Galenic form	Package size	Registered in	OTC since
Clotrimazole	Canesten [®]	Vaginal cream, 1%	6 pack	1980	1994
Clotrimazole	Canesten [®]	Vaginal cream, 10%	one	1986	1994
Clotrimazole	Canesten [®]	Pessaries, 100 mg	6 pack	1975	1994
Clotrimazole	Canesten [®]	Pessaries, 200 mg	3 pack	1982	1994
Clotrimazole	Canesten [®]	Pessaries, 500 mg	one	1983	1994
Clotrimazole	Canesten [®]	Combination pack	3 × 200 mg pessaries + 1% cream	1995	1995
Clotrimazole	Canesten [®]	Combination pack	1 × 500 mg pessary + 1% cream	1995	1995
Econazole	Pevaryl [®]	Pessaries, 50 mg	15 pack	1977	Rx only
Econazole	Pevaryl [®]	Pessaries, 150 mg	3 pack	1979	1993
Econazole	Pevaryl [®]	Vaginal cream, 1%	78 g	1977	1993
Econazole	Pevaryl [®]	Combination pack	3 × 150 mg pessaries + 1% cream	1994	1994
Econazole	Pevaryl Depot [®]	Pessaries, 150 mg	one	1985	1994
Econazole	Pevaryl Depot [®]	Combination pack	1 × 150 mg pessary (Depot) + 1% cream	1994	1994
Miconazole	Daktar [®]	Vaginal cream, 2%	50 g	1974	Rx only
Miconazole	Daktar [®]	Pessaries, 400 mg	3 pack	1981	Rx only
Fluconazole	Diflucan [®]	Capsules, 150 mg	one	1989	Rx only
Itraconazole	Sporanox [®]	Capsules, 100 mg	4 pack	1994	Rx only

OTC, over-the-counter; Rx, prescription

A continuous decline then occurred to approximately 53 000 packages sold in 1999, i.e. a 26% decrease. Econazole was the drug purchased predominantly, holding two-thirds of the market.

Both clotrimazole and econazole, applicable either as creams or vaginal suppositories, could be bought in Sweden as OTC products since 1994 and 1993, respectively. The sale of intravaginal preparations of these drugs in Skåne county during 1993–1994 was equal to 85–90 units/1000 women in the age group 15–60 years.

The sales volumes of packages of 150 mg fluconazole and packages with four capsules of 100 mg itraconazole, purchased between 1990 and 1999, are shown in Figure 2. These packages, both aimed for *per os* therapy of VVC and RVVC, held more than 90% of the market. Diflucan was introduced onto the market in 1989 and Sporanox in 1993. Figure 3 shows the sales of one-capsule packages of 150 mg fluconazole to different age groups in the county during the 1990s. Peak sales occurred in 1993. The number of packages sold per 1000 inhabitants was roughly the same over the study period, ranging from 5 to 35 packages, depending on consumer age group

(with the exception of the year 1993). The usage of packages containing four capsules of 100 mg itraconazole according to age group is illustrated in Figure 4. As evident from the figure, the sales volume for 1995 differed markedly from the other years studied.

DISCUSSION

To study the epidemiology of VVC and RVVC in an area by means other than analyzing the sales figures for drugs used to treat these infections is impossible. This is because, as evident from our study, the vast majority of episodes of these conditions are treated by the affected women themselves, by the use of OTC products. Thus, 93% of all drugs used for therapy of these conditions in the county, were sold over the counter.

The marked increase in sales of fluconazole in 1993 is most likely explained by a marketing campaign by the product manufacturer in that particular year, and is unlikely to reflect any change in the epidemiology of VVC and RVVC. The extreme sales volume in 1995 of packages

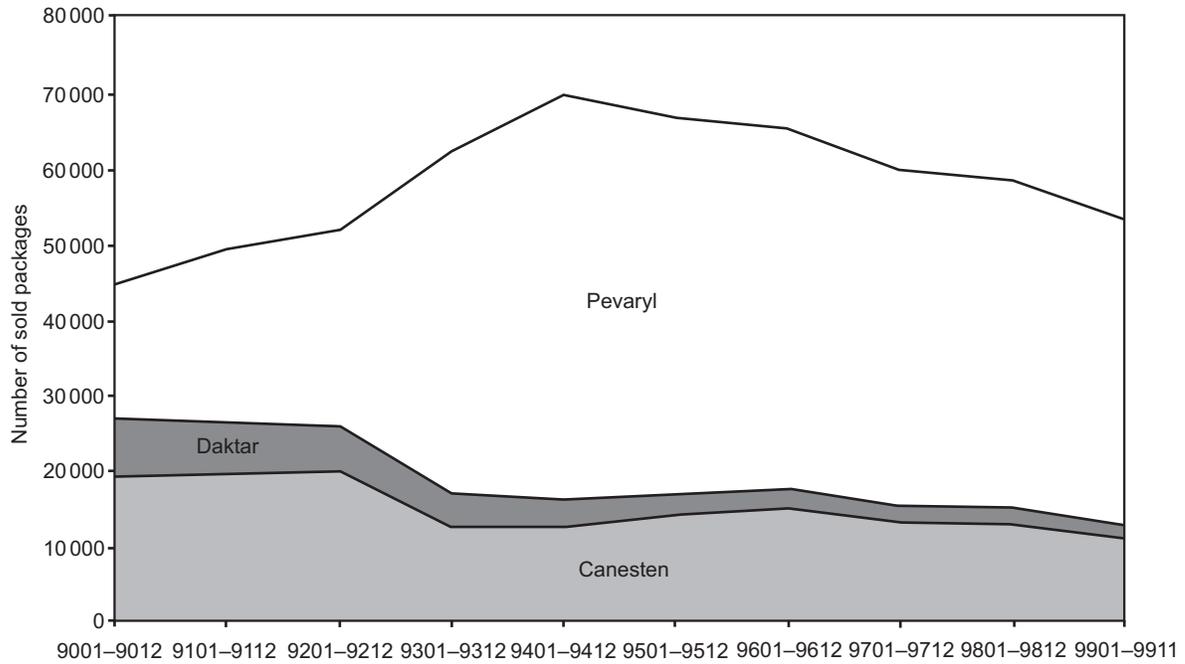


Figure 1 Total usage of vaginal preparations of econazole (Pevaryl[®]), miconazole (Daktar[®]) and clotrimazole (Canesten[®]), sold either by prescription or as over-the-counter products in Skåne county, Sweden, during the 1990s

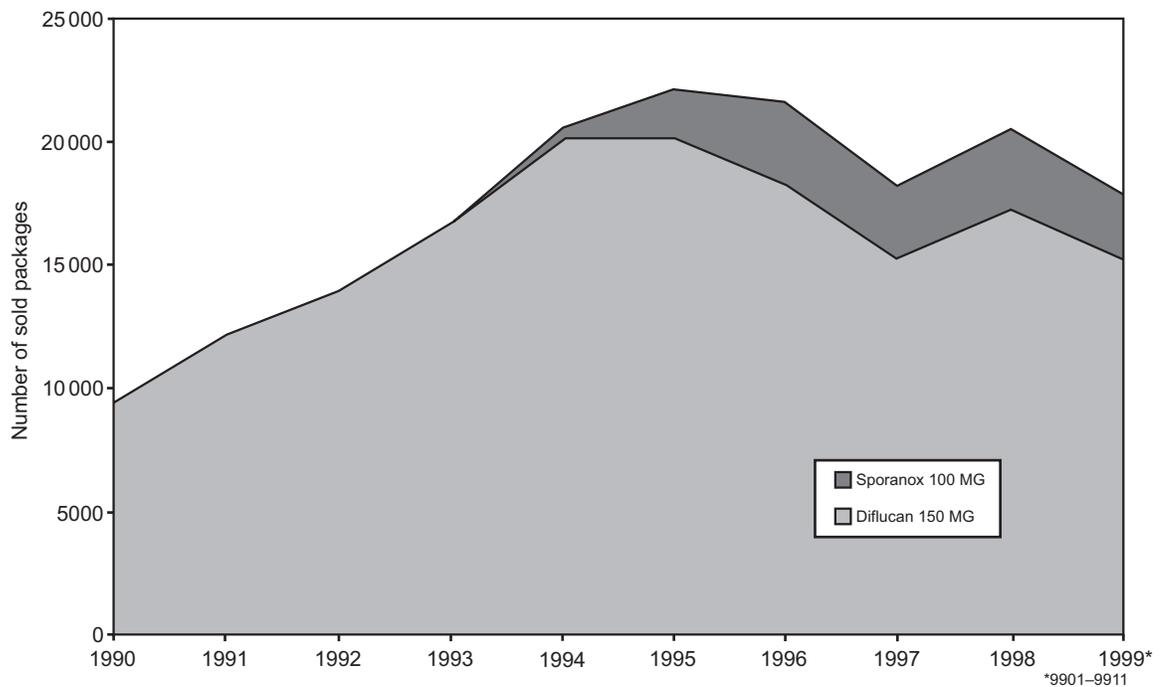


Figure 2 Number of prescriptions of 150 mg (single-dose) fluconazole (Diflucan[®]) and of four capsules of 100 mg itraconazole (Sporanox[®]), with genital *Candida* infection in females as the sole indication, sold in Skåne county, Sweden, during the 1990s

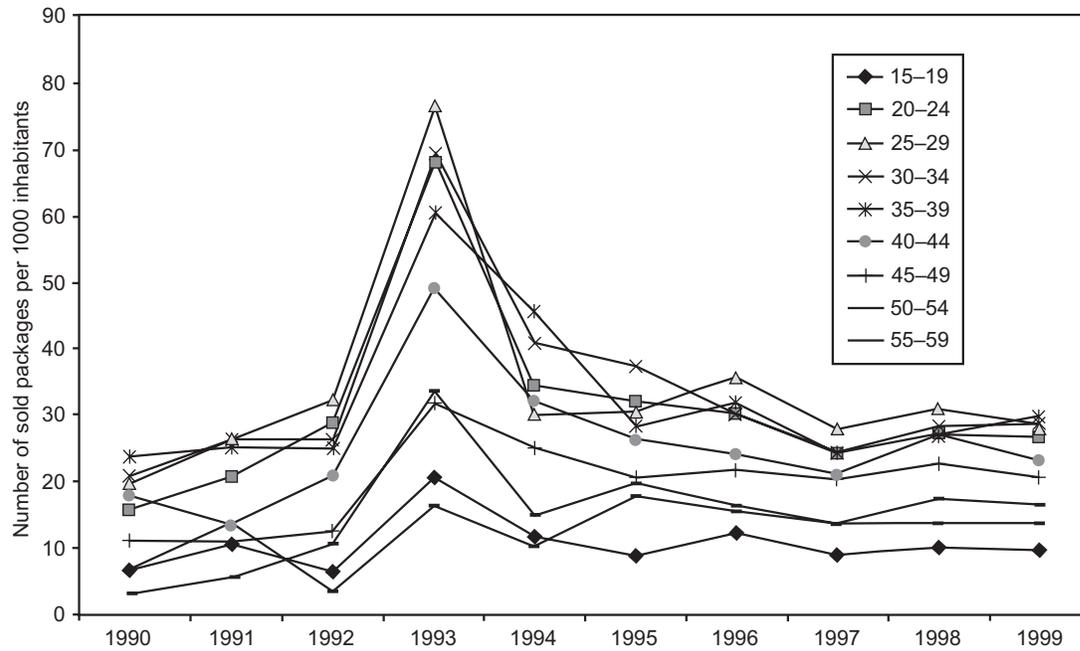


Figure 3 Number of prescriptions of one capsule of 150 mg fluconazole (Diflucan[®]) sold per age group in Skåne county, Sweden, during the 1990s

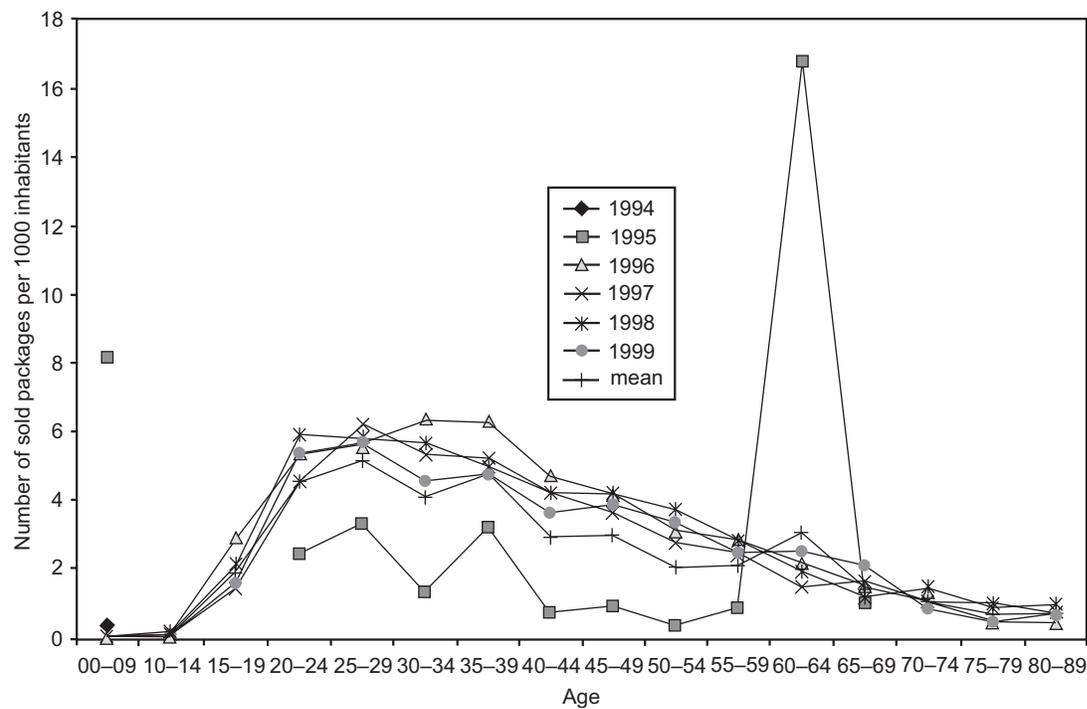


Figure 4 Number of prescriptions of four capsules of 100 mg itraconazole (Sporanox[®]) sold per age group in Skåne county, Sweden, during the 1990s

containing four capsules of 100 mg itraconazole (aimed for VVC/RVVC) is explained by the fact that only such packages were available for a new indication for the drug, namely for invasive (pulmonary) aspergillosis, which required such high dosages. Furthermore, our study shows that usage of four-capsule packages of itraconazole was mainly restricted to a small number of patients, i.e. in the age group 60–64 years. These examples illustrate that an unexpected rise in sales of an antifungal drug may be due to factors related to activities of the pharmaceutical drug industry, rather than to any change in the epidemiology of fungal infections.

A multifactorial explanation is likely for the changes over time seen in Skåne county in the sales of antifungal drugs for therapy of VVC/RVVC. It could involve demographic factors, e.g. alterations in the number of women living in the study area, particularly in age groups most susceptible to VVC and RVVC. However, there were only very small changes in the number of female inhabitants and their age distribution in the county during the 1990s.

Increased use of contraceptives, particularly of oral contraceptive pills containing gestagens and of hormone-releasing intrauterine devices (IUDs), could have contributed to an increased rate of VVC and RVVC and thereby to the changed sales volumes observed, as sex hormones stimulate germ tube formation (GTF) of *Candida* cells¹⁰ and extracellular matrix proteins may increase the chance of colonization of the vagina¹¹. GTF is a prerequisite for tissue invasion of yeast cells. The sales of oral contraceptives in Skåne increased by 20% during the 1990s, a trend that continued also at the latter part of the decade. Thus, these sales did not mirror those of the antifungal drugs. On the other hand, the purchase of hormone-releasing IUDs followed the increasing and decreasing trends in the sales volumes of the antifungal drugs over the decade. However, the number of IUDs sold ranged from only 2250 to 4500 per annum, with a sales peak of 14 000 devices for the 2-year period 1994–95.

Any increase in the prescription of hormone replacement therapy to postmenopausal women, which is known to enhance the rate of genital *Candida* infections¹², could also have resulted in a

greater usage of antifungal drugs. However, such prescriptions to postmenopausal women did not increase during the study period, although usage of high-dose estrogen preparations tripled during the 1990s. However, estrogen – in contrast to progesterone – may not influence GTF¹⁰.

The number of prescriptions of antifungal drugs used mainly for therapy of VVC/RVVC among the populations in the different municipalities in Skåne county showed great variation and was related to the density of the female population in the municipality, even after adjusting for the age of the inhabitants¹³. In comparison, the sales of all medical drugs to the same cohort of women in the different municipalities did not show any such trend. That is, usage of medical drugs in general was not higher in the mainly urban than in the mainly rural areas in the county, which was the case for the antifungals studied. The health-seeking behavior of urban and rural populations might differ, inhabitants in the former areas may more often consult for problems considered less serious, like genital *Candida* infections.

In Sweden, when a woman at telephone consultation reports symptoms suggestive of a genital *Candida* infection, a common recommendation is to buy an antifungal OTC product rather than to consult a physician. In the case that a woman attends a consultation, it will often occur with the involvement of a midwife (who is allowed to deal with these conditions and to prescribe drugs for local therapy of VVC). In the latter case, the national health insurance may pay the total cost of the drug or for some of it. Obviously, pharmacy counseling plays an important role in the management of VVC/RVVC.

Wide use of antifungal drugs has been discussed as one factor promoting the development of resistance in *Candida*^{14,15}, which may be an argument to reduce the present uncontrolled, liberal access to antifungal drugs as OTC products. On the other hand, OTC preparations for self-treatment of VVC and RVVC may, if used properly, provide patients with a faster cure at a lower cost^{16,17}. However, as mentioned, accurate diagnosis of VVC/RVVC by the patient herself, a physician or a counseling pharmacist, on

the basis of the case history alone, remains a problem. There seems to be a need for continuous postgraduate education of pharmacists and

other pharmacy employees on infectious conditions affecting the genital tract¹⁸.

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