PREVALENCE AND RISK FACTORS OF RADIAL RAY DEFICIENCIES

A population-based case-control study

Running title: RISK FACTORS OF RADIAL RAY DEFICIENCIES

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Funding

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Abstract

Radial ray deficiency is the most common congenital deficiency of the upper limb. The aim of our study was to investigate maternal risk factors for radial ray deficiencies. We conducted a nationwide population-based case-control study using national registers. All cases with a radial ray deficiency born between 1996 and 2008 were included in the study and compared with five controls without limb deficiency. In total, 115 (10 isolated, 18 with multiple congenital anomalies, and 87 syndromic) cases with radial ray deficiencies were identified and compared with 575 matched controls. The total prevalence in Finland was 1.22 per 10,000 births. No significant risk factors were observed for non-syndromic cases. In the syndromic group, advanced maternal age (≥35 years) increased the risk of radial aplasia (aOR 2.45, 95% CI 1.37–4.36), and a similar association was observed with multiple pregnancy (aOR 2.97, 1.16–7.62) and male sex (aOR 1.96, 1.18–3.25). Valproic acid was also a risk factor (*P*=0.002). In conclusion, novel associations in the syndromic group of advanced maternal age and multiple pregnancy and increased risk of radial ray deficiencies were observed. Also, early reports on increased risk of RRD associated with valproate and male sex were supported by our results.

Keywords: Maternal Age; antiepileptic; Radial Ray Deficiency; Risk Factor

Introduction

Radial ray deficiency (RRD) refers to a spectrum of congenital anomalies involving the radius, radial carpal bones, or thumb (Oberg et al., 2010). It is the most common congenital deficiency of the upper limb with reported prevalence ranging from 0.33 to 1.64 per 10 000 live births (Bednar et al., 2009; Ekblom et al., 2010; Froster and Baird, 1992; Goldfarb et al., 2006; Pakkasjarvi et al., 2013). Although both isolated and syndromic forms have been described, the majority of cases present with other major anomalies or syndromes, such as trisomy 18 (Pakkasjarvi et al., 2013; Stoll et al., 2013). Hence, infant mortality may be as high as 35% in bilateral RRD as a result of high frequency of underlying syndromes (Koskimies et al., 2011).

All RRDs can be included in the embryological class of formation defects, for which the primary event is a localized developmental failure due to genetic or non-genetic factors (Kozin, 2003). About half of radial disorders have a Mendelian cause and pattern of inheritance, whereas the remaining half appears sporadic with no known gene involvement. The genetics of radial deficiencies is complex, characterized by genetic heterogeneity and high inter and intra-familiar clinical variability (Elmakky et al., 2015)

Maternal use of valproic acid has been identified as a risk factor for RRDs and radial defects have been described as part of fetal valproate syndrome (Kikuchi et al., 2016; Langer et al., 1994; Rodriguez-Pinilla et al., 2000). Several risk factors for preaxial limb deficiencies have been reported, including smoking (Caspers et al., 2013), periconceptional alcohol consumption (Caspers Conway et al., 2014), and air pollution (Choi et al., 2019). However, RRD cases are often rare and sporadic. Hence, only few studies have addressed the risk factors of this anomaly specifically, and no population-based case-control studies on maternal risk factors of RRD are available.

Against this background, the aim of this study was to assess the national total prevalence and explore maternal and pregnancy-related risk factors for RRD. We hypothesized that first trimester medication use would increase the risk of radial ray deficiencies.

Methods

All cases (n=115) with congenital RRD born in Finland between Jan 1, 1996 and Dec 31, 2008 were identified from the National Register of Congenital Malformations, the Medical Birth Register, and the Register on Induced Abortions, all maintained by the Finnish Institute for Health and Welfare. Information on maternal prescription medicine use was obtained from the Register of Reimbursed Drug Purchases and the Register of Medical Special Reimbursements (Social Insurance Institution of Finland). These registers receive information based on a legally compulsory announcement request and have been validated as confirming accurate data with high coverage (Gissler et al., 1995; Leoncini et al., 2010; Pakkasjärvi et al., 2006).

A detailed description of the data collection for congenital limb deficiencies has been provided in previous papers (Koskimies et al., 2011; Syvänen et al., 2014). All cases with ICD-9 codes 75XX and

65XX from 1996 to 2008 were identified and reviewed. Identified matches were checked by the principal investigators and all cases other than radial ray deficiencies were excluded. Live births, stillbirths, and fetuses from spontaneous abortions and terminations of pregnancy due to fetal anomalies were included.

Five controls without limb deficiencies from the Medical Birth Register matched for residence, and time of conception (± 1 month) were randomly selected for each case. For the terminated fetuses, live-born controls without limb deficiencies were selected.

Maternal risk factors in the register were analyzed including maternal age, BMI, parity, smoking, documented long-term diseases (Diabetes Mellitus, Asthma, Psychotic Mental Conditions, Depression, Epilepsy, and Inflammatory Bowel Diseases based on information on the right to free medication), history of miscarriages, and infertility treatments including in vitro fertilization. Smoking was defined as active smoking during the first trimester. Maternal weight was recorded at the first prenatal visit 8–10 weeks after conception. The initial analysis of maternal medication was done at the fourth level of the Anatomical Therapeutic Chemical (ATC) Classification System by WHO. Each drug group with at least five exposed mothers was studied in univariate logistic regression and significant risk factors in these analyses were included the multivariable model. Antiepileptic drugs were further analyzed independently as valproic acid (ATC-5: N03AG01) has been reported to be associated with increased risk of RRD (Kikuchi et al., 2016; Langer et al., 1994; Rodriguez-Pinilla et al., 2000).

Conditional logistic regression was used to evaluate different risk factors. First, univariate models were programmed, and Fisher's exact test was executed to identify potential risk factors. Subsequently, a multivariable model was created. Odds ratios (OR) along with adjusted odds ratios (aOR) with 95% confidence intervals (CI) were calculated. The analyses were performed using SAS System, version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

Ethical Considerations

The approval of the Institutional Review boards at the Finnish Institute of Health and Welfare and Turku University Hospital were obtained before conducting this study.

Results

There were 115 cases of congenital radial ray deficiencies including 11 (11/115, 9.6 %) stillbirths and 36 (36/115, 31.3 %) elective terminations of pregnancy. The total prevalence was 1.22 per 10,000 births and the live birth prevalence was 0.76 per 10,000 live births. No significant trend in prevalence was observed in any of the subgroups of RRD analyzed (Figure 1). Fourteen of the live born infants died during the first week of life and 13 died during the first year of life. The perinatal mortality rate was 316 per 1,000 births. The infant mortality rate was 397 per 1,000 live births. Our cohort of 115 radial ray deficiencies included 87 cases with syndromic background, 10 isolated cases, and 18 cases with multiple congenital anomalies (MCA).

Syndromic cases

In total, there were 87 cases of syndromic RRD, and these were compared with 435 matched controls. Among syndromic patients, there were 39 cases of Trisomy 18, 17 VACTERL associations, three Rapadilino and Goldenhaar syndromes, two fetal valproate syndromes, two patients with Trisomy 13, and 21 cases with other or unknown syndromes. In univariate analyses, advanced maternal age (≥35 years) was identified as a significant risk factor for RRD, OR 2.55, 95% CI 1.48–4.41. Also, multiple pregnancy (OR 2.81, 95% CI 1.15–6.83) and male sex (OR 1.85, 95% CI 1.14–3.02) increased the risk of RRD. Other maternal risk factors were not significantly associated with increased risk. All potential risk factors with sufficient number of cases for statistical analyses are presented in Table 1.

Maternal use of progestogens (ATC code G03D) increased the risk of RRD in univariate analysis (OR 2.63, 95% CI 1.03–6.75). Similarly, antiepileptics (OR 7.50, 95% CI 1.25–44.89) and valproic acid (*P* = 0.002) were significant risk factors. Due to known etiology, two cases with valproate syndrome were excluded from other analyses. No significant associations were found with other maternal medications (Table 2). All prescription drugs analyzed are presented in Annex 1.

Significant risk factors for syndromic cases in univariate analysis were entered into a multivariable model. Non-significant factors were subsequently removed separately. Prematurity was not considered as a risk factor but rather a reflection of a pregnancy with an anomaly, and hence was not included in the multivariable model. Multivariable analysis confirmed the increased risk associated with advanced maternal age (aOR 2.45, 95% CI 1.37–4.36). RRDs were also significantly associated with male sex (aOR 1.96, 95% CI 1.18–3.25) and multiple pregnancy (aOR 2.97, 95% CI 1.16–7.62) – Figure 2.

Non-syndromic cases

There were 28 cases with non-syndromic RRD including 10 isolated and 18 MCA cases and these were compared with 140 matched controls. In univariate analyses none of the risk factors were significant in the group without syndromic background. Only primiparity (OR 2.20, 95%CI 0.97-4.98) and male sex (OR 2.12, 95%CI 0.87-5.14) suggested associations. All analyzed and potential risk factors for non-syndromic RRD are presented in Table 3.

Discussion

In this large population-based case-control study we observed that advanced maternal age was associated with syndromic RRD. Similarly, male gender and multiple pregnancy were associated with increased risk. Valproic acid medication during the first trimester of pregnancy was also a significant risk factor for RRD. On the other hand, no significant associations were found with RRD without syndromic or chromosomal background.

Our data on exposures and outcomes were prospectively collected by the universally accessible healthcare system of our country. The registers used in this study were complete with accurate and validated data and the coverage during the study years is high (Gissler et al., 1995; KELA; Koskimies et al., 2011; Leoncini et al., 2010; Pakkasjärvi et al., 2006; Syvänen et al., 2014). The diagnosis of each

RRD was confirmed by the principal investigators and controversial cases were discussed by two experienced pediatric orthopedic surgeons. The case-control design was selected to identify risk factors for very rare clinical conditions. As most cases had chromosomal or syndromic background (76%), our study lacks the power to analyze risk factors for isolated and MCA groups.

Our study also supports the few earlier findings of associations between valproic acid and RRD. Both of our cases with valproate exposure had diagnosis of fetal valproate syndrome in the register. Also, an association was observed between maternal special reimbursements for epilepsy and syndromic radial ray deficiencies. A Norwegian study (Klungsoyr et al., 2019), however, reported no significant association between epilepsy and congenital limb deficiencies. Consistent with our results, valproic acid therapy has previously been associated with limb deficiencies and RRD has been described as a part of valproate syndrome (Langer et al., 1994; Rodriguez-Pinilla et al., 2000).

Advanced maternal age was significantly associated with increased risk of RRD in our study. To the best of our knowledge, this association between advanced maternal age and increased risk of RRD is a novel finding. However, advanced maternal age is a known risk factor for chromosomal abnormalities (Harris et al., 2017; Zhang et al., 2017) as well as non-chromosomal birth defects (Harris et al., 2017). According to earlier studies, only 8–30% of RRD cases are isolated (Goldfarb et al., 2006; Koskimies et al., 2011) and half the cases are associated with known syndromes or chromosomal anomalies (Pakkasjarvi et al., 2013). Hence it is logical that advanced maternal age is also a risk factor for RRD.

Live birth prevalence was 0.76 per 10,000 live births, and consistent with previous reports (Aro et al., 1982; Bednar et al., 2009; Froster and Baird, 1992; Kallen et al., 1984; Pakkasjarvi et al., 2013). Also, male preponderance of RRD cases has likewise been reported in earlier studies (Froster and Baird, 1992; James et al., 1999; Robert et al., 1997). We found no earlier reports on the association of multiple pregnancy and the risk of RRD. However, in the study by Robert et al. (1997), twinning rate was found to be higher in preaxial defects compared to the population rate. Also, multiple pregnancy is a well-established risk factor for several other birth defects (Layde et al., 1980; Li et al., 2003; Mastroiacovo et al., 1999; Tang et al., 2006)

There are early reports of an association of maternal use of exogenous sex hormones and various congenital malformations including limb deficiencies (Czeizel et al., 1983; Heinonen et al., 1977; Janerich et al., 1974). As progestogens are often used in assisted reproductive technology, earlier studies have failed to demonstrate whether the increased risk of anomalies is associated with the hormone itself, the technology used, or the maternal and paternal factors related to subfertility (Berntsen et al., 2019). In our data, infertility treatments were not associated with radial ray deficiencies. However, this data was not available for terminated pregnancies, which may be a source of bias. Our data suggest that progestogens may be associated with increased risk of RRD. Previously, progestogens have been also reported to be a risk factor for limb deficiencies associated with amniotic bands (Syvänen et al., 2020). However, the association with RRD was not significant in the multivariable model.

In our study, there were 28 non-syndromic cases and our findings on the risk factors are mainly based on the syndromic cases, namely monogenic disorders. It is well known that older mothers have a

higher risk of chromosomal anomalies such as Down syndrome (Hollier et al., 2000; Sherman et al., 2007). This is in accordance with our findings. Male sex has been identified as a risk factor for several congenital anomalies, as we also observed in syndromic RRD (Black et al., 2020; Tennant et al., 2011). In the literature, higher frequency of non-chromosomal congenital anomalies has been reported among multiple births (Boyle et al., 2013). On the other hand, multiple birth does not appear to increase the risk of chromosomal anomalies (Boyle et al., 2013). In our data, however, multiple pregnancy was associated with syndromic deficiencies but not with non-syndromic RRD. Boyle et al. (2013) speculated that this risk could be caused by artificial reproductive therapy, which was not a significant risk factor for RRD in our data. Our findings are hence limited by the possibility that the risk factors observed may be associated with either increased risk of chromosomal disorders or RRD or both.

Strengths and Limitations

The strength of the study was the use of high-quality, validated, and prospectively collected register data with total population coverage (Artama et al., 2011). The diagnosis of each RRD case was confirmed by reviewing relevant patient records. Also, our study included stillbirths and terminations of pregnancy. The main limitation of our study was a relatively small sample size, especially among non-syndromic cases. Additionally, we were limited by the paucity of data collected in the Register of Induced Abortions and by the reliance of the study solely on the accuracy of the register data.

In conclusion, early reports on the increased risk of RRD associated with valproic acid were supported by our results. Also, increased risk of RRD, especially with syndromic background, appears to be associated with advanced maternal age, male sex, and multiple pregnancy.

Acknowledgements

Dr Raitio, Dr Helenius and Dr Syvänen report grants from Clinical Research Institute HUCH, and Dr Helenius reports grants and personal fees from Medtronic, grants from K2M, outside the submitted work. Also, we would like to thank Drugs and Pregnancy project for their co-operation with this study.

Conflict of Interest

None

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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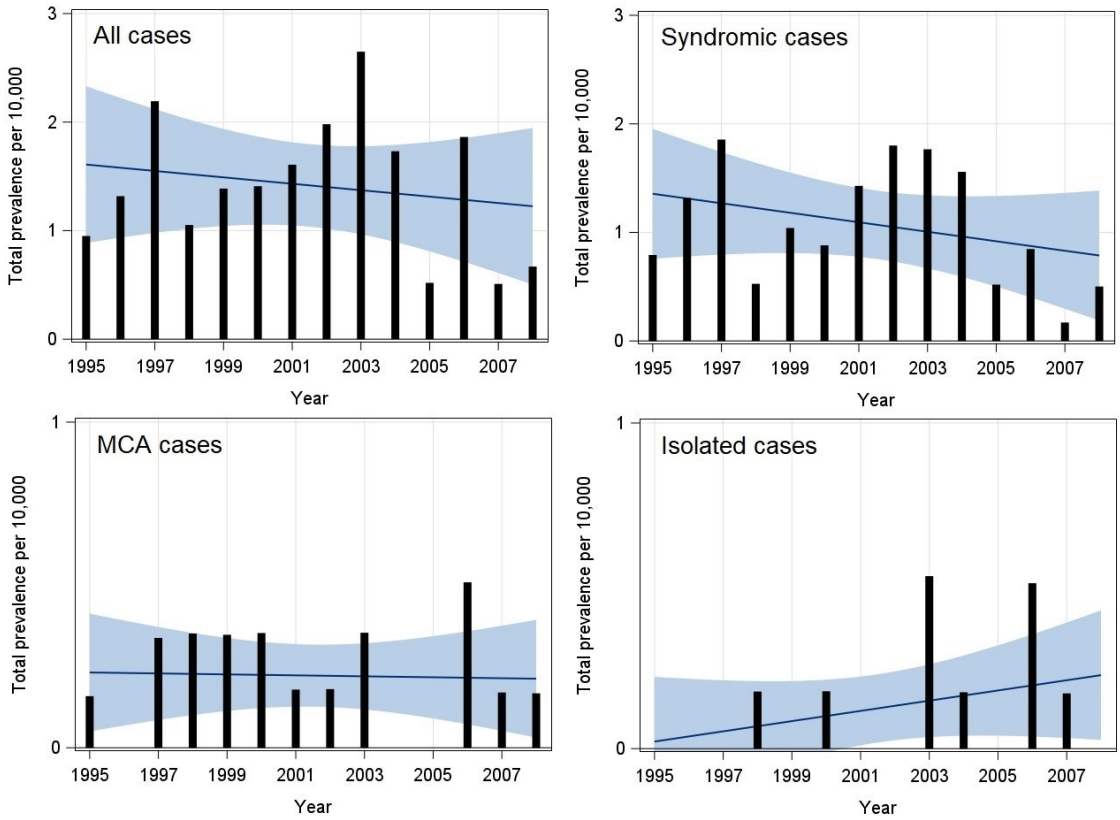

Figure 1. Prevalence of RRD cases among different subgroups with no significant trend over time. Linear regression with confidence interval presented with line and blue area, respectively.

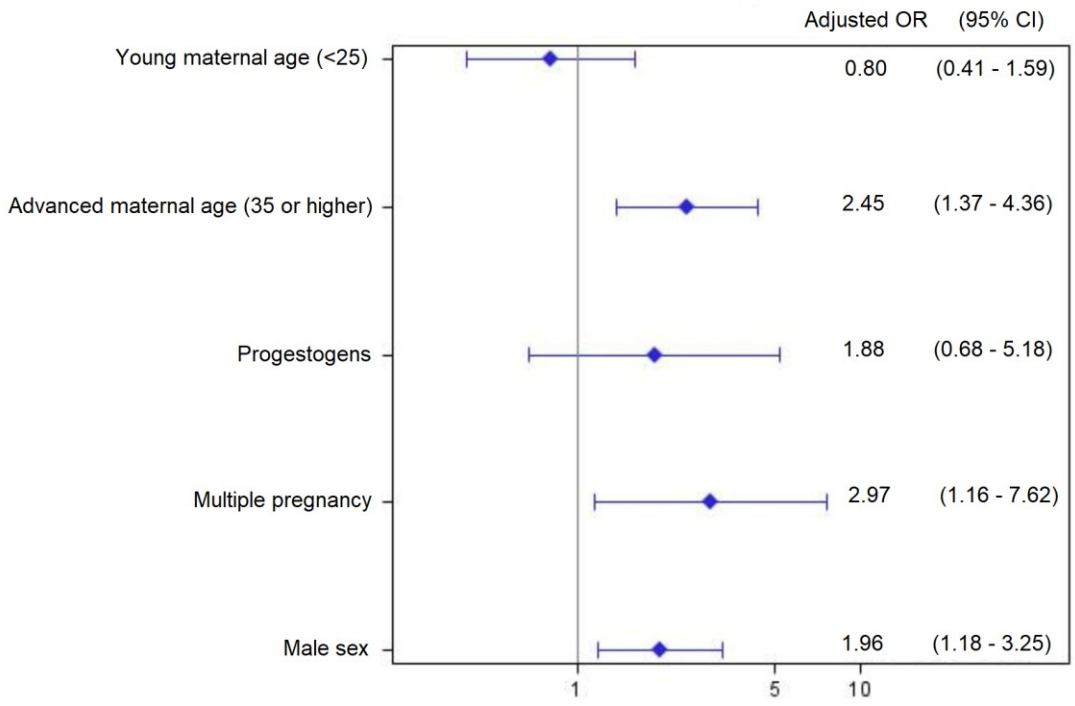

Figure 2. Multivariable analysis of the risk factors for syndromic RRD adjusted for risk factors presented in the figure.

	Number of Events		Odds ratio	95% CI
	Cases (n=87)	Controls (n=435)		
Maternal Age <25 years (ref 25 – 34)	13 (14.9%)	91 (20.9%)	0.88	0.45–1.70
Maternal Age ≥35 years (ref 25 – 34)	27 (31.0%)	62 (14.3%)	2.55	1.48–4.41
Nulliparity	33 (37.9%)	176 (40.5%)	0.89	0.55–1.46
Pregestational diabetes	1 (1.1%)	6 (1.4%)	1.30	0.14–10.12
Epilepsy	3 (3.4%)	2 (0.5%)	7.73	1.27–46.95
Asthma	1 (1.1%)	16 (3.7%)	0.30	0.04–2.33
Smoking	7 (8.0%)	70 (16.1%)	0.70	0.30–1.61
Multiple pregnancy	8 (9.2%)	15 (3.4%)	2.81	1.15–6.83
Assisted reproductive technology *	3 (4.9%)	15 (3.4%)	1.70	0.45–6.49
Invasive fetal investigation	6 (6.9%)	22 (5.1%)	1.73	0.66–4.50
Prematurity	55 (63.2%)	24 (5.5%)	50.00	19.23–125.00
Male sex	57 (65.5%)	227 (52.2%)	1.85	1.14–3.02

Table 1. Univariate analysis of maternal risk factors for syndromic radial ray deficiencies.
*includes missing values among cases

Exposure (ATC code)	Number of Events		Odds ratio	95% CI
	Cases (n=87)	Controls (n=435)		
Valproic acid (N03AG01)	2 (2.3%)	- (0%)	N/A	N/A
Antiepileptic drugs (N03A)	3 (3.4%)	2 (0.5%)	7.50	1.25–44.89
Beta blockers (C07A)	1 (1.1%)	2 (0.5%)	2.50	0.23–27.57
Estrogens (G03C)	2 (2.3%)	4 (0.9%)	2.50	0.46–13.65
Progestogens (G03D)	7 (8.0%)	14 (3.2%)	2.63	1.03–6.75
Gonadotropins (G03G)	5 (5.7%)	16 (3.7%)	1.60	0.57–4.48
Muscle relaxants (M03B)	1 (1.1%)	6 (1.4%)	0.83	0.10–6.92

Table 2. Univariate analysis of the association of prescription drugs and syndromic radial ray deficiencies. N/A – data not available

	Number of Events		Odds ratio	95% CI
	Cases (n=28)	Controls (n=140)		
Maternal Age <25 years (ref 25 – 34)	8 (28.6%)	28 (20.0%)	1.94	0.72–5.21
Maternal Age ≥35 years (ref 25 – 34)	6 (21.4%)	19 (13.6%)	2.13	0.72–6.29
Nulliparity	15 (54.6%)	48 (34.3%)	2.20	0.97–4.98
Pregestational diabetes	1 (3.6%)	- (0%)	N/A	N/A
Epilepsy	- (0%)	- (0%)	N/A	N/A
Asthma	- (0%)	5 (3.6%)	N/A	N/A
Smoking	3 (17.7%)	15 (11.2%)	2.03	0.46–8.96
Multiple pregnancy	1 (3.6%)	2 (1.4%)	2.50	0.23–27.57
Assisted reproductive technology*	- (0%)	3 (2.1%)	N/A	N/A
Invasive fetal investigation	- (0%)	4 (2.9%)	N/A	N/A
Prematurity	13 (46.4%)	8 (5.7%)	16.13	4.55–58.82
Male sex	19 (70.4%)	74 (52.9%)	2.12	0.87–5.14

Table 3. Univariate analysis of maternal risk factors for non-syndromic radial ray deficiencies.
*includes missing values among cases
N/A – data not available

Annex 1. List of all analyzed ATC drug groups with exposures among case or control mothers.

ATC code	Name of the drug group
A02B	DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE
A03F	PROPULSIVES
A07E	INTESTINAL ANTIINFLAMMATORY AGENTS
A10A	INSULINS AND ANALOGUES
B01A	ANTITHROMBOTIC AGENTS
C07A	BETA BLOCKING AGENTS
D01A	ANTIFUNGALS FOR TOPICAL USE
D06B	CHEMOTHERAPEUTICS FOR TOPICAL USE
D07A	CORTICOSTEROIDS, PLAIN
D10A	ANTI-ACNE PREPARATIONS FOR TOPICAL USE
G01A	ANTIINFECTIVES AND ANTISEPTICS, EXCL. COMBINATIONS WITH CORTICOSTEROIDS
G03C	ESTROGENS
G03D	PROGESTOGENS
G03G	GONADOTROPINS AND OTHER OVULATION STIMULANTS
H01C	HYPOTHALAMIC HORMONES
H02A	CORTICOSTEROIDS FOR SYSTEMIC USE, PLAIN
H03A	THYROID PREPARATIONS
J01A	TETRACYCLINES
J01C	BETA-LACTAM ANTIBACTERIALS, PENICILLINS
J01D	OTHER BETA-LACTAM ANTIBACTERIALS
J01F	MACROLIDES, LINCOSAMIDES AND STREPTOGRAMINS
J01M	QUINOLONE ANTIBACTERIALS
J02A	ANTIMYCOTICS FOR SYSTEMIC USE
L02A	HORMONES AND RELATED AGENTS
M01A	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS
M03B	MUSCLE RELAXANTS, CENTRALLY ACTING AGENTS
N02B	OTHER ANALGESICS AND ANTIPYRETICS
N02C	ANTIMIGRAINE PREPARATIONS
N03A	ANTIEPILEPTICS
N05A	ANTIPSYCHOTICS

N05B	**ANXIOLYTICS**
N06A	**ANTIDEPRESSANTS**
P01A	**AGENTS AGAINST AMOEBIASIS AND OTHER PROTOZOAL DISEASES**
R01A	**DECONGESTANTS AND OTHER NASAL PREPARATIONS FOR TOPICAL USE**
R01B	**NASAL DECONGESTANTS FOR SYSTEMIC USE**
R03A	**ADRENERGICS, INHALANTS**
R03B	**OTHER DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES, INHALANTS**
R05D	**COUGH SUPPRESSANTS, EXCL. COMBINATIONS WITH EXPECTORANTS**
R05F	**COUGH SUPPRESSANTS AND EXPECTORANTS, COMBINATIONS**
R06A	**ANTIHISTAMINES FOR SYSTEMIC USE**
S01G	**DECONGESTANTS AND ANTIALLERGICS**