Adverse reactions after substitution of dexamphetamine

Introduction

Dexamphetamine (Amfexa®) is indicated *as part of a comprehensive treatment program for attention deficit / hyperactivity disorder (attention deficit hyperactivity disorder or ADHD) in children and adolescents from 6 to 17 years, when the response to previous treatment with methylphenidate is not clinically satisfactory*. An extensive treatment program usually consists of psychological, pedagogical and social measures. Amfexa® was granted a Marketing Authorization on 20 October 2014. In July 2020, the manufacturer changed the name Amfexa® to Tentin®[1].

In the Netherlands, many patients were started on pharmacy compounded dexamphetamine, before Amfexa® became available. In 2019 the Inspectorate for Healthcare and Youth (IGJ) reported that they had investigated whether pharmacists who prepare dexamphetamine themselves and deliver it to other pharmacists adhere to all conditions for delivery of compounded dexamphetamine. An important principle of the Circular on Compounded products (Circulaire 'handhavend optreden bij collegiaal doorleveren van eigen bereidingen door apothekers' 2019-01-IGZ) is that collegial resale is only permitted if there is clear added value of the resupplied preparation. This added value must be described by the preparatory pharmacy in a product file and depends on two factors; 1. absence of registered adequate alternatives and 2. a clear pharmacotherapeutic rationale. Both factors must be laid down in a structured way by the preparatory pharmacy, ending with a clear conclusion. From this conclusion it must be apparent for which therapeutic objective(s) and in which patient population(s) the preparation provided has added value (indication(s)). The added value must be based on a special need of a medical nature. In addition, the added value of the supplied preparation must be clearly stated in the accompanying product information for healthcare provider and / or patient. The investigation showed that for dexamphetamine the above mentioned conditions are not (always) adhered to[2].
The IGJ noted that dexamphetamine is available in the Netherlands as the registered product Amfexa®, nowadays marketed as Tentin®. This medicine is only available in 5 milligram tablets. Pharmacies can only deliver the compounded product to patients if there is no suitable registered alternative. This means that most patients can use the registered product. For a small group of patients, namely children from 3 to 6 years with ADHD, a lower dose is regularly prescribed. Because there is a special need of a medical nature, compounded preparations for this patient group may be supplied. In some other cases too, there may be a medical necessity for a compounded drug, such as in patients with an allergy to an excipient[2]. The IGJ investigation led to many additional patients being switched from the compounded dexamphetamine to Amfexa® in 2019.
In July 2020, the manufacturer changed the name Amfexa® to Tentin®. The manufacturer stated that they changed the name, but the product remained the same. Contrary to Amfexa®, a Tentin®-tablet can be divided in four equal parts[1]. This implicates that the need to deliver dexamphetamine as compounded preparation will cease to exist in case of dosing issues.

This signal is an update of the previous signal from December 2019, which described 65 cases of substitution of dexamphetamine[3].

Reports

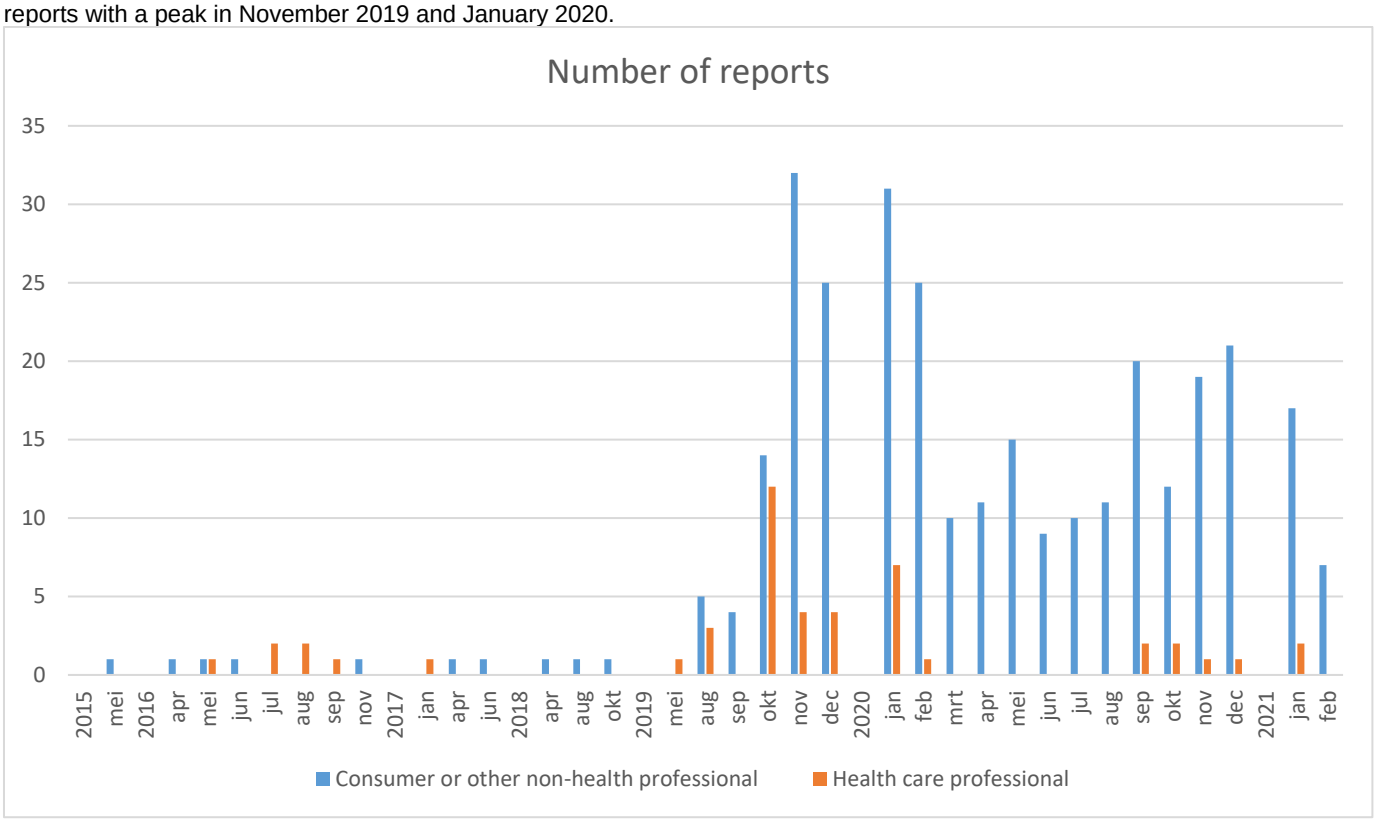
From 2015 until 18 February 2021 the Netherlands Pharmacovigilance centre Lareb received 350 reports of ADRs after drug substitution of dexamphetamine. In 183 of these reports, it was reported that the dexamphetamine was withdrawn (52%). Based on this large number of reports, the data is presented in Tables and Figures. Table 1 shows that the number of reports increased over the years and most reports were reported by consumers (n=308).

Table 1. Reports of substitution of dexamphetamine per year and reporter.

Receive date	Consumer	Health care professional	Total
2015	1	0	1
2016	4	6	10
2017	2	1	3
2018	3	0	3
2019	80	24	104
2020	194	14	208
2021 (until 1 March 2021)	24	2	26
Total	308	47	355*

*This number is higher than 350 since 5 reports are reported by consumers as well as health care professionals.

Figure 1 shows the number of reports per months and type of reporter. From August 2019 there is an increase in reports with a peak in November 2019 and January 2020.



Most commonly reported ADRs are depressed mood, headache and palpitations. The top 20 of most commonly reported ADRs is shown in Table 2. It can be seen that the most commonly reported ADRs are all listed in the Summary of Product Characteristics except for ineffectiveness of the drug (SmPC)[1].

Table 2. Most commonly reported ADRs (MedDRA preferred terms)

ADRs		SmPC
Depressed mood	111	Yes
Headache	100	Yes
Palpitations	54	Yes
Disturbance in attention	51	Yes
Restlessness	41	Yes
Insomnia	37	Yes
Drug ineffective	37	No
Fatigue	36	Yes
Dizziness	34	Yes
Nausea	31	Yes
Irritability	28	Yes
Aggression	27	Yes
Anxiety	26	Yes
Decreased appetite	21	Yes
Agitation	17	Yes
Abdominal pain	17	Yes
Dry mouth	17	Yes

Sleep disorder	14	Yes
Mood swings	14	Yes
Affect lability	13	Yes

Table 3 lists the ADRs that were reported ≥ 3 times and were not listed in the SmPC[1]. It can be seen that lack of efficacy is mentioned the most. Multiple (MedDRA®) ADR terms describe a lack of efficacy: Drug ineffective, Therapeutic product effect decreased, Therapeutic product effect incomplete, Therapeutic response decreased, Drug effect less than expected and Condition aggravated.

Table 3. ADRs (MedDRA preferred terms) reported ≥ 3 times and not listed in the SmPC

ADRs	
Drug ineffective	37
Migraine	8
Therapeutic product effect decreased	8
Rebound effect	6
Therapeutic product effect incomplete	6
Trismus	6
Bruxism	6
Constipation	5
Dyspnoea	5
Muscle tightness	4
Pruritus	4
Therapeutic response decreased	4
Listless	4
Hyperacusis	4
Drug effect less than expected	3
Tinnitus	3
Social avoidant behaviour	3
Hot flush	3
Personality change	3
Condition aggravated	3
Binge eating	3
Malaise	3
Dyspepsia	3
Crying	3
Diplopia	3
Musculoskeletal stiffness	3

Table 4 lists the substitution from the dexamphetamine product (left column) that was used in the past, to the suspect drug that was causing the ADRs (columns 2-5). Most substitutions concern the substitution of Dexamphetamine with an unknown brand to Amfexa® (n=202).

Substitution					
	AMFEXA	**ATTENTIN**	**DEXAMPHETAMINE Brand unknown**	**TENTIN**	**Total**
AMFEXA TABLET 5MG				13	13
DEXAMPHETAMINE Ace pharmaceuticals				4	4
DEXAMPHETAMINE Ceban	6		1	1	8
DEXAMPHETAMINE DMB	57		2	18	77
DEXAMPHETAMINE Fagron	1				1
DEXAMPHETAMINE Brand unknown	202	5	6	38	251
DEXAMPHETAMINE Pharmaline	4			1	5
DEXAMPHETAMINE Verenigde Apotheken Limburg			1		1
Total	**270**	**5**	**10**	**75**	**360***

*This total is higher than 350 reports, since some patients mention more than one suspect drug.

Table 5 lists the substitution from the dexamphetamine product (left column) that was used in the past, to the suspect drug that was causing Lack of efficacy (PT terms: Drug ineffective, Therapeutic product effect decreased, Therapeutic product effect incomplete, Therapeutic response decreased, Drug effect less than expected and Condition aggravated. (columns 2-5).

Lack of efficacy					
	AMFEXA	**ATTENTIN**	**DEXAMPHETAMINE Brand unknown**	**TENTIN**	**Total**
AMFEXA TABLET 5MG				1	1
DEXAMPHETAMINE Ace pharmaceuticals				1	1
DEXAMPHETAMINE Ceban	1				1
DEXAMPHETAMINE DMB	10		1	3	14
DEXAMPHETAMINE Brand unknown	36	1	1	6	44
Total	**47**	**1**	**2**	**11**	**61**

Prescription data

Data from Stichting Farmaceutische Kengetallen indicates that the portion of compounded dexamphetamine decreased from 30% in the first six months of 2020 to 17% in October 2020 9 (see Figure 2).

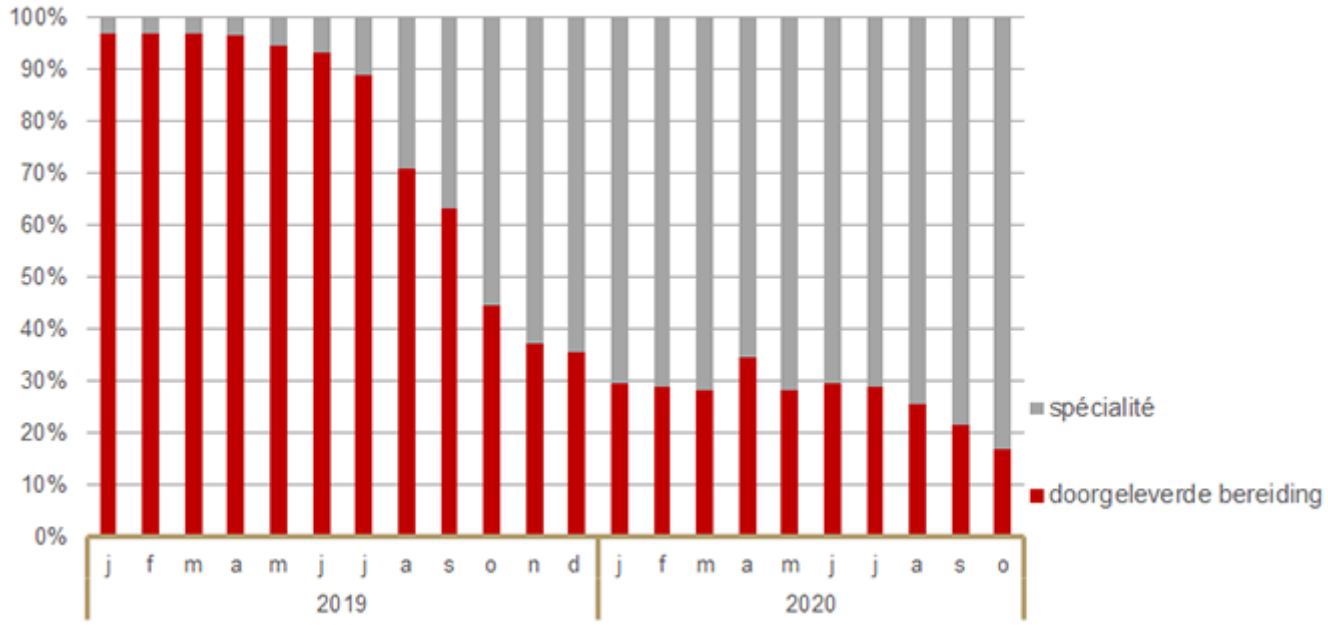


Figure 2. Share (%) in number of DDD of dexamphetamine (N06BA02) provided by product group[4].

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb noticed a sharp increase in the reports on Amfexa®, related to ADRs after drug substitution, since the IGJ reported on the terms of delivery for compounded dexamphetamine in July 2019[2], with a peak in November 2019 and January 2020. Since then, the number of reports concerning substitution remains high. Until 18 February 2021, 350 spontaneous reports of ADRs after substitution of dexamphetamine were received.

Most commonly reported ADRs are depressed mood (n=111), headache (n=100) and palpitations (n=54). These are ADRs that are mentioned in the SmPC. Remarkable are reported decreased effects and ineffectiveness (n=61) .

A clear pattern in the reports after substitution is missing. The extent to which there are differences in pharmacokinetics and stability between Amfexa® or Tentin® and compounded dexamphetamine products, that could be responsible for the reported reactions, is as yet unclear. In theory, differences in dissolution could cause differences in bioavailability. Attention is warranted for possible negative effects in patients switching of dexamphetamine.

Literature

1.College ter Beoordeling van Geneesmiddelen. Dutch SmPC Tentin® [updated 08-07-2020]. Available from: https://www.geneesmiddeleninformatiebank.nl/smpc/h124800_smpc.pdf.
2.Inspectie voor Gezondheidszorg en Jeugd. Bereidende apotheken voldoen niet aan voorwaarden bij doorlevering dexamfetamine 2019 [updated 01-07-2019]. Available from: https://www.igj.nl/actueel/nieuws/2019/07/01/bereidende-apotheken-voldoen-niet-aan-voorwaarden-bij-doorlevering-dexamfetamine
3.Adverse reactions after switch from compounded dexamfetamine to Amfexa®. Bijwerkingen Centrum Lareb. Available from: https://databankws.lareb.nl/Downloads/Signals_2019_ADRs_switch_compounded-dexamfetamine_Amfexa.pdf
4.Dexamfetamine steeds vaker als specialite verstrekt. Stichting Farmaceutische Kengetallen. Available from: https://www.sfk.nl/publicaties/PW/2020/dexamfetamine-steeds-vaker-als-specialite-verstrekt

This signal has been raised on June 23, 2021. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl