Adolescents' perspectives on chronic medication use: opportunities for mHealth

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Colophon

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Adolescents' perspectives on chronic medication use: opportunities for mHealth

Perspectief van adolescenten op hun chronisch geneesmiddelgebruik: mogelijkheden voor mHealth

(met een samenvatting in het Nederlands)

Proefschrift

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	Dr. T.W. de Vries

The most effective way to do it, is to do it

— *Amelia Earhart* —

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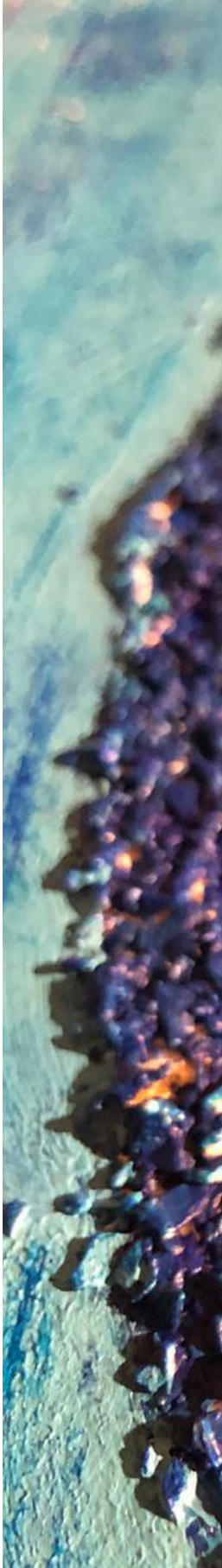

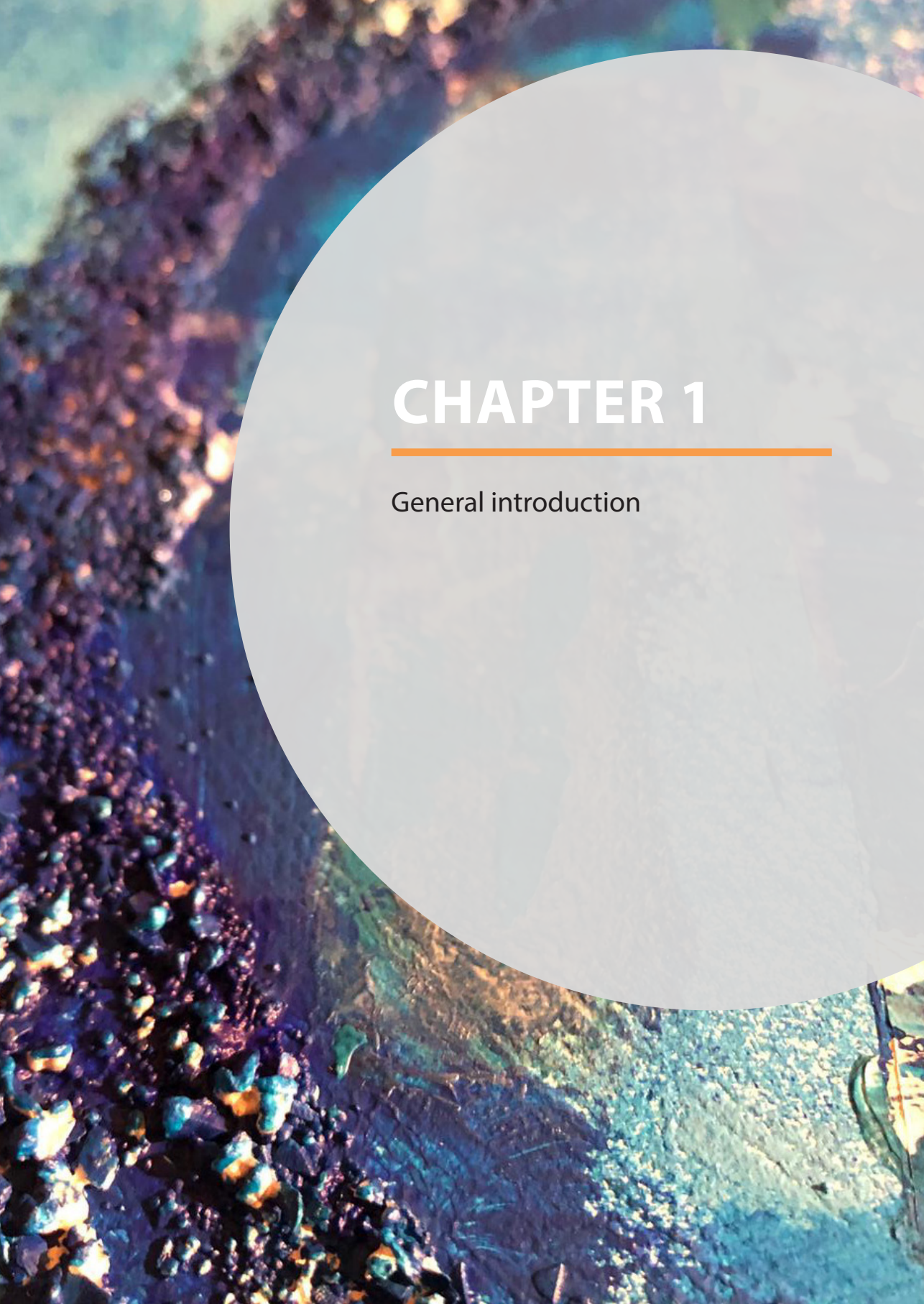

CHAPTER 1

General introduction

Adolescence (age 12 - 18 years) is a life phase in which many unique physical, psychological, and social changes occur.[1] During this time children become independent individuals, thus their parental supervision gradually decreases, while their own responsibilities increases.[2] A decrease in motivation is often experienced, and peers are of utmost importance for adolescents. Adolescence is also associated with risk-taking behaviour related to alcohol and substance use, sexual activity, and school leavings.[1,3] In general, adolescence is seen as a difficult age period, while their habits, beliefs, perceptions, and attitudes might sustain into adulthood. Here are huge opportunities for healthcare providers to improve healthcare.

Adolescents often do not receive appropriate attention in healthcare. They are classified within paediatrics, while adolescents face unique barriers and have their own needs and preferences.[4,5] For example, adolescents believe more in overuse of medication than in the general harm of medicines.[6] Healthcare providers should pay extra attention to this age group,[7] because investments in adolescent's understanding of their chronic condition and their treatment, are a first step toward life-long correct disease management.[5,7]

ADOLESCENTS USING CHRONIC MEDICATION

Chronic illnesses among adolescents are an important public health concern. Around 10% of adolescents have a chronic condition, and for example the number of adolescents with attention-deficit/hyperactivity disorder (ADHD) has almost doubled in the last 20 years.[8,9] Chronic illnesses may have both physical and emotional consequences for patients, such as pain, the feeling of being left out, or prolonged stress.[10] Having a chronic disease also encompasses changes in the everyday routine of patients, for example taking medication, lifestyle changes, monitoring symptoms, and attending clinical controls.[8] Therefore, having a chronic illness has a major impact on patient's life, especially for adolescents who are in a developmental phase of their life.

This thesis focuses on the perceptions of adolescents with a chronic condition, which is important as they become independent individuals. Many previous studies in adolescents also took the opinion of parents into account, as parental illness perception strongly influence adherence during childhood.[11] Moreover, parents still play a role during adolescence, for example, family support can reduce adolescents' negative attitudes towards medication and healthcare providers, which improves asthma control and quality of life.[12] However not all parents have the drive to achieve high adherence, or they have ineffective problem-solving behaviour themselves.[13] Additionally, the parental supervision gradually decreases over time, and previous studies showed discrepancies between parents and adolescents regarding adherence, asthma symptoms, or the impact of the disease on adolescents' life.[14,15] It is therefore important to focus on adolescents in healthcare and target interventions on them. Parents may be involved, but the first focus should be on the adolescent.

The most common chronic paediatric conditions are eczema, asthma, and ADHD.[16] These conditions often require daily medication use for prolonged periods, described below. The extent to which the prevalence of diseases change during adolescence is currently not extensively investigated.[17]

Eczema

Eczema, also known as atopic dermatitis, is an inflammation of the skin which is characterized by itching and recurrent eczematous lesions. It is highly prevalent in young children (~20%), more in girls than in boys, and it gradually decreases towards adulthood, with a prevalence rate of approximately 3% during adolescence.[18-20] Daily use of emollients and moisturizers is recommended to hydrate the skin and protect it from potential irritants. Moreover, intermittent use of topical corticosteroids (TCS) is prescribed during exacerbations,[21-23] varying from weak to very potent.[24] Medication adherence among eczema patients is often low and complicated,[25,26] due to the different application techniques, cosmetic aspects, lack of knowledge on how to use the treatment, and the fear of side effects, i.e. corticophobia.[27,28]

Attention-deficit/hyperactivity disorder

ADHD is a neuropsychiatric disorder characterized by problems paying attentions, excessive activity, or difficulties with controlling behaviour.[29,30] ADHD is diagnosed in 3% of the children and adolescents, and it is more prevalent in boys than in girls.[31] Besides behavioural therapies, stimulant medication is the main pharmaceutical treatment. In the Netherlands, the number of ADHD medication users increases every year, with 222,975 users in 2016. In 2017, there was a turning point, as the number of users slightly decreased (1%) to 219,699.[32] There was a 5.6% decrease for users aged 6 to 15 years resulting in 85,000 users in 2017.[33] Short-acting and long-acting methylphenidate are the preferred stimulant medication for ADHD, thereafter dexamphetamine. An alternative non-stimulant therapy is atomoxetine.[30]

Asthma

Asthma is a chronic inflammation of the airways characterized by wheezing, coughing, chest tightness, and shortness of breath, which may vary over time and intensity. Around 10% of the children worldwide is diagnosed with asthma.[34,35] During childhood, asthma is more prevalent in boys, while during adolescence wheezing becomes more prevalent in girls, and this continues into adulthood.[36] Environmental factors (e.g. allergen exposure, smoke, and, animals), exercise, stress, and infections can trigger asthma symptoms and may result in an asthma exacerbation. The stepwise treatment approach (***Figure 1***) for asthma starts with using a short-acting beta-agonist (SABA) as needed. For patients with persistent asthma symptoms, daily use of inhaled corticosteroids (ICS) is subsequently prescribed. When patients remain uncontrolled, a long-acting beta-agonist (LABA) may be added to the treatment. Further therapeutic options in severe asthma are leukotriene antagonists (LTRA).[34,37] Effective asthma management is important to control asthma symptoms. However uncontrolled asthma is common, mostly because of medication non-adherence, poor inhaler techniques, or exposure to triggers. To ensure an effective treatment, it is important to

regularly assess the diagnosis (e.g. asthma or allergic rhinitis), review patient's medication use (e.g. inhaler technique), adjust the treatment when needed (e.g. stepping up or stepping own), and review the treatment response.[34]

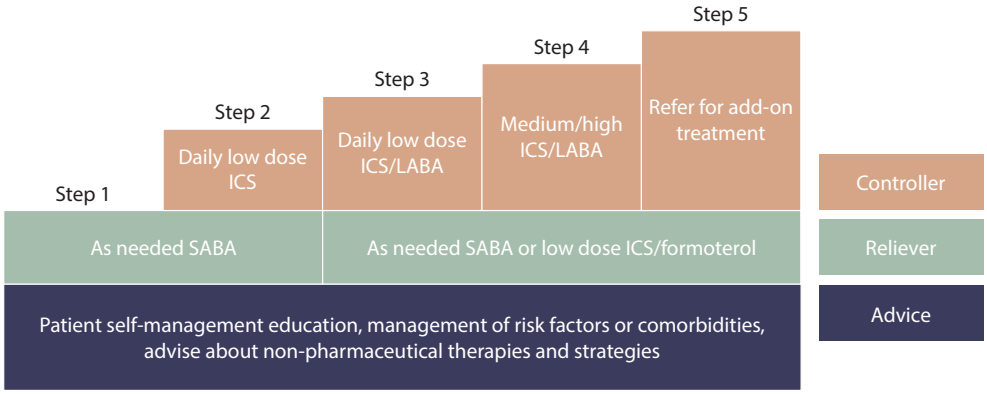

Figure 1. Stepwise approach for asthma treatment (adapted from the global initiative for asthma [GINA] 2018).[34]
ICS, inhaled corticosteroids; SABA, short-acting beta-agonist; LABA, long-acting beta-agonist.

MEDICATION ADHERENCE

Medication non-adherence is a common, costly, and complex problem in healthcare worldwide. On average 50% of patients who suffer from chronic conditions are adherent to their treatment.[38-40] It has been suggested that non-adherence is especially a problem in adolescents.[41] Adherence (***Table 1***) is driven by several intentional and unintentional factors (***Figure 2***).[42,43] Intentional non-adherence refers to the decision-making process of the patient to take medication (or not). Patient's beliefs, such as necessity and concerns about medication, are important here.[44,45] Unintentional non-adherence is related to unplanned behaviour and may be the result of forgetfulness or misunderstanding. Complexity of treatment and patient's memory play a major role in here.[46] Unintentional non-adherence is in particular relevant for adolescents as they are prone to forget things and they prefer to focus on the current moment, i.e. short-term outcomes instead of long-term goals, as their prefrontal cortex is still in development.[47,48] Additionally, the decrease in parental supervision and poor medication and disease knowledge, might also contribute to the increased percentage of non-adherent patients during adolescence.[2,49] However, the exact reasons for the increase in non-adherence during adolescence is unclear.

Table 1. Definitions by the World Health Organization (WHO)

Term	Definition
Adherence	The extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes – corresponds with agreed recommendations' from a healthcare provider[40]
eHealth	Electronic health is the use of information and communication technologies (ICT) for health[50]
mHealth	Mobile health is the use of mobile devices to support medical and public health practice, examples are mobile phones, patient monitoring devices, personal digital assistants, and other wireless devices[51]

Non-adherence is not only driven by multiple factors (***Figure 2***),[52] it also occurs at different stages, which makes it even more complex. First of all, there is a proportion of patients who do not collect their prescribed medication regimen. Secondly, some patients do not start taking their prescribed medication (initiation), and lastly there is a large proportion of patients who does not continue to use their medication as prescribed (implementation and persistence).[53,54] The latter is in particular important for patients with chronic diseases.

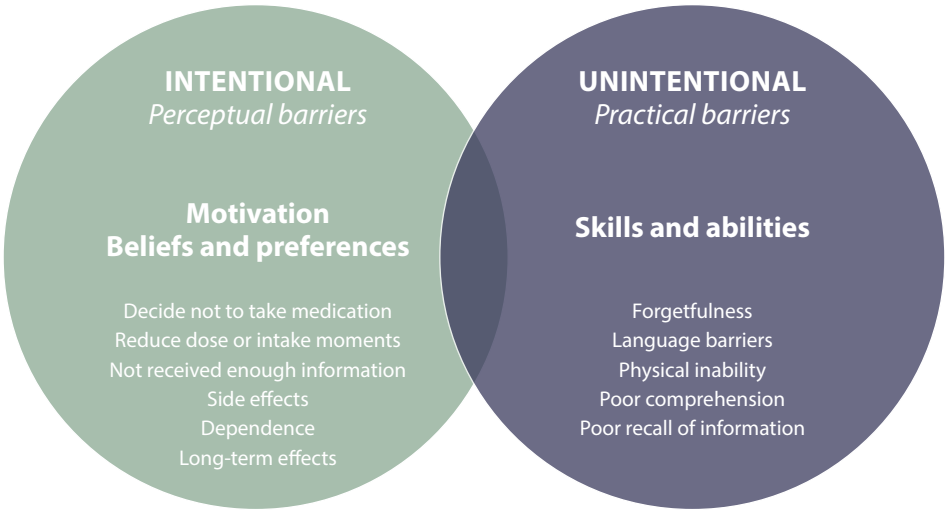

Figure 2. Adherence model (adapted from Horne 2009).[55]

Not taking medication as prescribed has major consequences for patients. The US Surgeon General Charles Everett Koop (1985) stated *"Drugs don't work in patients who don't take them"*. Non-adherence can result in less disease control, successively resulting in a decreased quality of life, increased use of healthcare resources (e.g. medication and hospitalizations), and even deaths. Altogether, non-adherence also increases healthcare costs for society.[56] It has been estimated that in the US alone, non-adherence results in 300 billion of avoidable costs in the healthcare system and 125,000 avoidable deaths.[57] It is therefore important to measure and monitor adherence. There are several methods to measure adherence. First, there is a direct measurement, where adherence can be measured via the presence of a biological marker in body fluids, via direct observation of patient's medication behaviour, or via ingestible sensors. Secondly, databases such as medication refill records can be used. Different methods to calculate adherence based on records are developed. Thirdly, self-report is often used, such as diaries and questionnaires. Various questionnaires are developed and validated. Fourthly, electronic medication packaging devices are developed. These packages register the dose taken by a patient. And lastly, pill counting can be done to see if patients are adherent or not.[58] All these methods differ in accuracy and different biases come along, therefore there is no gold standard for measuring adherence.

ADHERENCE-ENHANCING INTERVENTIONS

For many years, researchers focused on interventions to improve medication adherence.[59] Several interventions targeting different aspects of non-adherence behaviour have been developed. For example, interventions increasing patient's disease and treatment knowledge, interventions addressing patients concerns and necessity beliefs about the treatment,[59,60] and interventions improving medication intake behaviour by using specific types of drug packages, such as multidose dispensing systems or electronic medication packaging devices.[61,62] Medication reminders are also developed to improve adherence, as forgetfulness is a major cause of non-adherence.[63-65] Previous studies showed that simple interventions, targeting one aspect of non-adherent behaviour, are not effective.[64,66] Therefore most adherence interventions are complex and consist of several elements targeting different aspects of non-adherent behaviour. However, there is also still inconsistent evidence for complex adherence interventions.[59,60,65]

Digital interventions

Digital technology plays an important role in the development of affordable and feasible adherence interventions. Nowadays, most adherence interventions are technology mediated interventions, e.g. digital reminders or informational websites. The field of electronic health (eHealth; ***Table 1***) is rapidly developing,[50] because eHealth contains promising functionalities for medication management; it supports personalisation, tailoring, and patient monitoring.[46,67,68] In particular, mobile health (mHealth; ***Table 1***) interventions have the potential to support medication adherence,[51] because mHealth is interactive, adaptive, persuasive, potentially cost-effective, and more than 70% of the

population in Western Europe own a smartphone.[69-71] MHealth is therefore increasingly used and it is highly appreciated by patients, as the usability, feasibility, and acceptability of mHealth interventions are high.[70] There is some evidence that mHealth interventions improve self-management and health outcomes.[71,72] However, the effectivity of digital interventions to enhance adherence is still inconsistent.[73,74]

Currently not many mHealth interventions are developed for adolescents,[59,75,76] while almost all adolescents (>95%) own a smartphone and have a positive attitude towards mobile technology.[77,78] MHealth for adolescents should contain behavioural and educational components, as educational interventions alone are inefficient in improving adherence among adolescents.[66] Moreover, the focus should be on control beliefs, as these are associated with self-management in adolescents with chronic diseases.[45] Altogether, more research toward the development and effectiveness of mHealth in adolescents is needed.

COMMUNITY PHARMACY

In the Netherlands, every patient is registered at a single pharmacy and usually fills all their prescriptions in this pharmacy. Pharmacists are medication experts, who are responsible for medication counselling (which is obligated when medication is dispensed for the first time) and adherence, and thereby improving quality of patient care and disease outcomes. Currently, the role of community pharmacists is shifting from a management role, i.e. the distribution of medicines, to a more healthcare providing role, i.e. conducting medication reviews.[79,80] In addition, patients have the last healthcare provider contact in the pharmacy, before they start using (or continue to use) their medication. The community pharmacy might therefore be the right place for interventions aiming at adherence, as pharmacists can act as a medication counsellor.

During adolescence, children go less often to their physician, and they are not often seen in the pharmacy, because their parents mostly collect their medication.[81,82] It is therefore hard to reach adolescents, and pharmacists could not act as a mediation counsellor for them. An interactive pharmacy-based mHealth intervention might bridge this gap and it has the potential to support adherence and self-management. Positive effects of pharmacy delivered mHealth interventions are shown for the disease management of several chronic conditions in adults.[83,84] However, not many mHealth interventions are developed in pharmacies, and they did not focus on adolescents at all.[70-72]

OBJECTIVES

The overall aim of this thesis was to study adolescents' perspectives on chronic medication use and to evaluate the effect of a pharmacy-based mHealth intervention to support adherence and self-

management in adolescents with a chronic disease. The focus was on the most common chronic conditions among adolescents, i.e. asthma, atopic dermatitis, and ADHD.

The following objectives were defined:

- To assess overall drug use among adolescents;
- To explore the beliefs, experiences, and preferences of adolescents with atopic dermatitis towards their treatment;
- To gain more insight into the attitudes of adolescents with ADHD towards their treatment;
- To study the associations between illness perceptions, medication beliefs, medication adherence, disease control, and quality of life in adolescents with asthma;
- To develop a mHealth intervention supporting adherence and self-management among adolescents;
- To evaluate the effectiveness of the ADolescent Adherence Patient Tool (ADAPT), an interactive mHealth intervention, in supporting self-management and improving ICS adherence in adolescents with asthma;
- To explore the use and effective engagement of adolescents with the ADAPT intervention;
- To explore experiences, barriers, and facilitators of pharmacists and patients towards the use of the ADAPT intervention;
- To study the normalization potential of a complex mHealth intervention for adolescents with asthma in the community pharmacy.

OUTLINE OF THIS THESIS

Chapter 2 *"Medication used by adolescents"* describes which medication is used among adolescents and how medication use changes during adolescence, based on medication refill records.

Chapter 3 *"Adolescents' perspectives on chronic medication use"* focuses on the most frequently prescribed chronic medications shown in ***Chapter 2***. In ***Chapter 3.1*** the beliefs, experiences, and preferences of adolescents with atopic dermatitis towards their treatment are explored. ***Chapter 3.2*** gives more insights into medication use and attitudes of adolescents with ADHD. ***Chapter 3.3*** provides insights in the medication use of adolescents with asthma and shows the associations between illness perceptions, medication beliefs, adherence, asthma control, and quality of life.

Chapter 4 *"Mobile health intervention for adolescents with asthma"* focuses on the development and testing of an interactive mHealth intervention for adolescents with asthma to support self-management and adherence. ***Chapter 4.1*** describes the rationale and design of the ADAPT study. The effectiveness of the ADAPT intervention on adherence, asthma control, and quality of life is shown in ***Chapter 4.2***. ***Chapter 4.3*** describes the use and the effective engagement of adolescents with the ADAPT intervention.

Chapter 5 *"Implementation of mHealth in the community pharmacy"* focuses on the evaluation and integration of the ADAPT intervention in clinical practice. In ***Chapter 5.1*** we evaluated the ADAPT intervention among patients and pharmacists, and in ***Chapter 5.2*** we applied a theoretical framework to study the normalization potential of the ADAPT intervention in a community pharmacy setting.

Finally, ***Chapter 6*** contains a general discussion, in which the results of all studies are summarized and put into a broader perspective with recommendations for future research. We also explored the opportunities for mHealth in healthcare and provided recommendations for effective use of mHealth in clinical practice.

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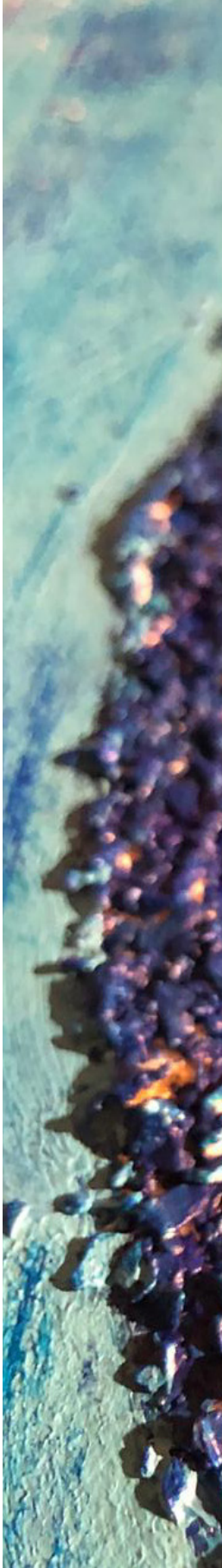

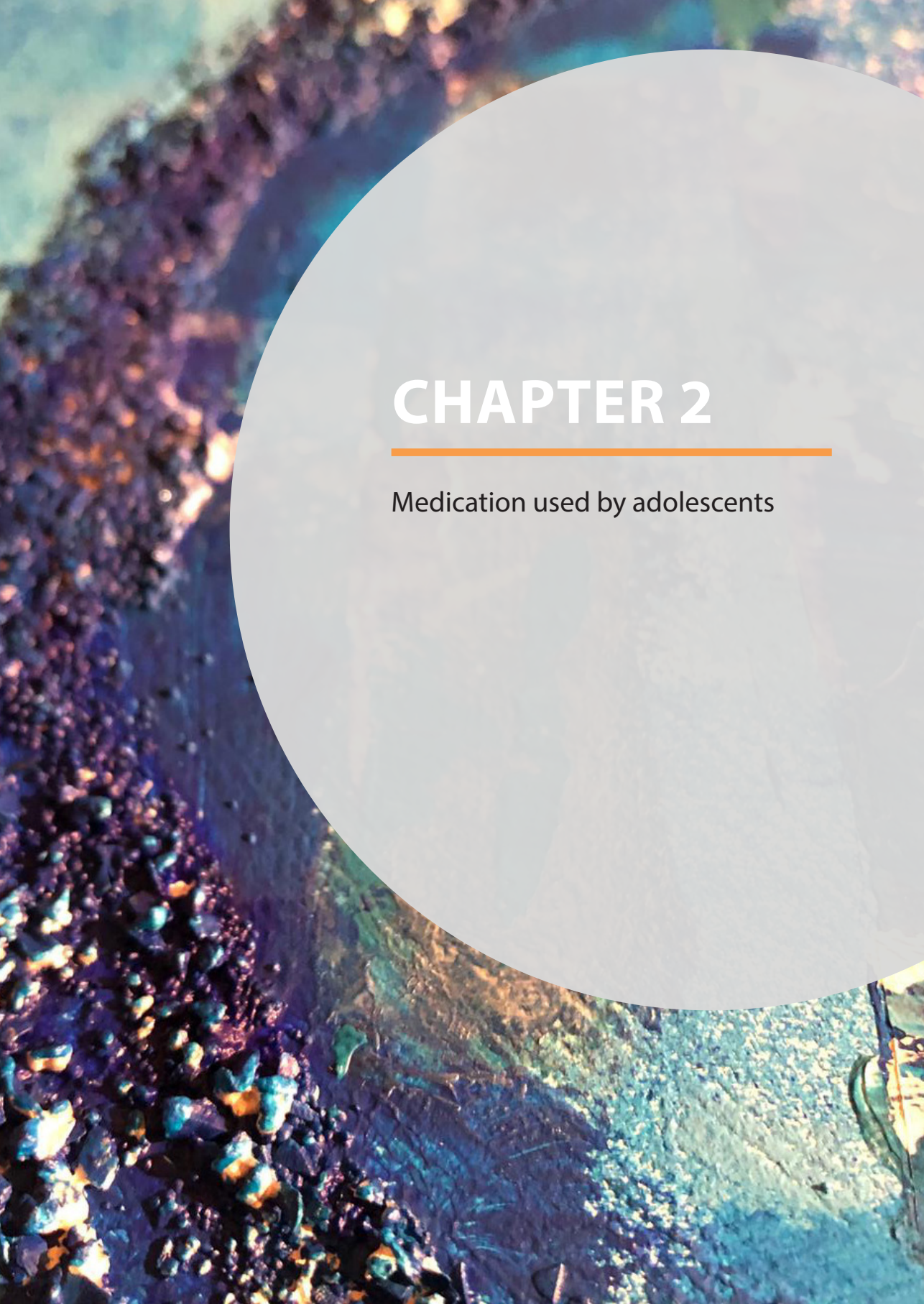

CHAPTER 2

Medication used by adolescents

CHAPTER 2.1

Drug utilisation among Dutch adolescents: a pharmacy prescription records study

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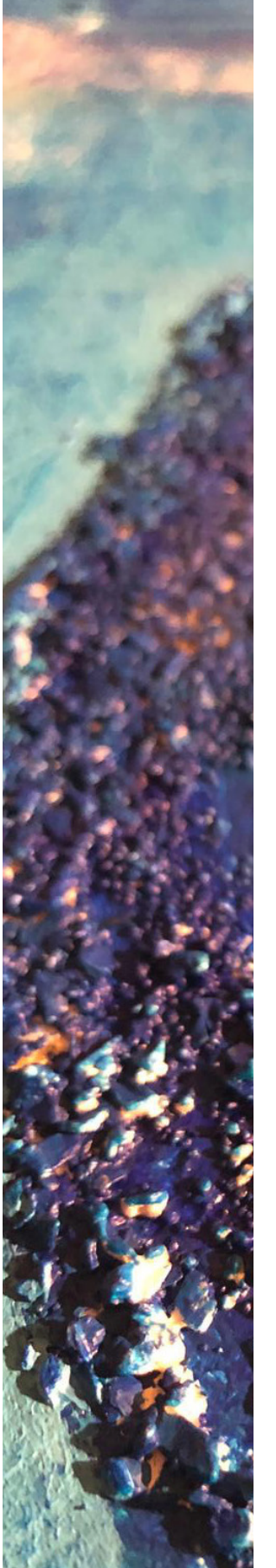

ABSTRACT

Background: Studies on adolescent drug use are scarce as most studies do not distinguish between children and adolescents. Therefore, we assessed overall drug use in adolescents.

Methods: A retrospective cohort study was conducted using pharmacy dispensing records from 62 community pharmacies in the Netherlands. Dispensing records of the previous five years were extracted for adolescents (age 12 - 18 years).

Results: The study population consisted of 47,421 adolescents who collected at least one medication prescription during adolescence (mean age 15.5 ± 1.8 years; 48.9% males). Half of them collected dermatologicals (46.2% males; 52.3% females), followed by drugs for the respiratory system (43.4% males; 40.3% females) and anti-infectives for systemic use (31.3% males; 39.1% females). The percentage of males using dermatologicals slightly increased, while the percentage of female users decreased with age. The most prescribed active ingredient was methylphenidate.

Conclusions: These insights into adolescent drug use help us to better understand adolescent healthcare use.

INTRODUCTION

Studies on drug use among adolescents are scarce. Many drug utilisation studies do not distinguish between children and adolescents,[1] while adolescence is an interesting life phase: children start making their own choices, become responsible for their medication regimen and drug use increases during this period.[2-5]

It is important to know what kind of medication is used by adolescents to get a better understanding of adolescents' healthcare utilisation and needs. Therefore, we aimed to assess overall drug use among adolescents aged 12 - 18 years, with a focus on different ages and sexes.

METHODS

Study design and data collection

We conducted a retrospective cohort study using pharmacy dispensing records. Data were obtained from Dutch community pharmacies as part of the ADolescent Adherence Patient Tool study,[6] approved by the Medical Review Ethics Committee of the University Medical Centre Utrecht (NL50997.041.14) and registered at the Dutch Trial Register (NTR5061). Dispensing records of the previous five years were extracted from adolescents aged 12 - 18 years at the time of inclusion (between July 2015 and May 2016). These records contained information on date of birth, sex, drug name, amount, dosage, prescription date, and Anatomical Therapeutic Chemical (ATC) classification codes.[7] Personal data, such as name and address, were not extracted, ensuring privacy of individuals.

Database

Duplicates, records with administrative errors and prescriptions for non-medications such as dressing materials were excluded. Moreover, prescriptions collected before the age of 12 were excluded. We divided the ATC codes into five levels to create an overview: anatomical main group, therapeutic subgroup, pharmacological subgroup, chemical subgroup, and chemical substance.[7]

Analysis

Microsoft Excel 2010 and Microsoft Access were used for data management. Statistical analyses were performed using IBM SPSS for Windows, V.23.0. First, we calculated descriptive statistics. For skewed data, the median with IQR is shown instead of the mean with SD. Thereafter, non-parametric Mann-Whitney and Kruskal-Wallis tests were used to compare differences between gender and age groups. P-values <0.05 were considered statistically significant.

RESULTS

In total, 79,398 adolescents were registered at 62 pharmacies. At the time of inclusion, 58,923 patients (74.2%) collected at least one medication prescription in the previous five years.

We excluded 10,465 patients who only had a prescription before the age of 12 years, and 1,037 patients who only collected non-medications (e.g. dressing materials). Therefore, our final study population consisted of 47,421 adolescents (59.7% of total) who collected at least one medication prescription during adolescence. Their mean age was 15.5 ± 1.8 years and 48.9% (n=23,170) were males.

The total number of collected prescriptions was 539,096, and the median number of collected prescriptions per person was 5 (IQR 11) during an average period of 2.7 ± 1.7 years. The individual adolescents received prescriptions for medications within 1 - 12 ATC groups (median 2; IQR 3). The highest number of prescriptions were for the nervous system, respiratory system and dermatologicals, and the most collected active pharmaceutical ingredient was methylphenidate, that is, 72,077 prescriptions (***Table 1***). Females mostly collected drugs for the genito urinary system and sex hormones, followed by dermatologicals and medicines for the respiratory system.

When looking at the prevalence rates (***Table 2***), half of the study population collected at least one prescription for dermatologicals. Medication prescriptions for the respiratory system and anti-infectives for systemic use were also collected by many adolescents. The most collected number of prescriptions within dermatological preparations (D07) were for triamcinolone (D07AB09; 25.1%) and for hydrocortisone (D07AA02; 20.8%). Most collected prescriptions for obstructive airway diseases (R03) were salbutamol (R03AC02; 45.6%) and fluticasone (R03BA05; 22.2%). Desloratadine (R06AX27; 51.6%) and levocetirizine (R06AE09; 26.0%) were the most collected (third-generation) antihistamines for systemic use (R06). Within antibacterials for systemic use (J01), amoxicillin (J01CA04; 19.8%), nitrofurantoin (J01XE01; 13.5%) and doxycycline (J01AA02; 12.8%) were mostly collected.

One-third of the adolescents collected prescriptions for the alimentary tract and metabolism (***Table 2***), which were mostly prescriptions for sodium fluoride (A01AA01; 21.7%) or macrogol combinations as laxatives (A06AD65; 12.3%). The prescriptions for the nervous system were mainly for methylphenidate (N06BA04; 53.0%) or melatonin (N05CH01; 10.7%).

Almost half of the adolescent females collected drugs for the genito urinary system and sex hormones (***Table 2***), which increased over time from 7% to 73% (age 12 - 18 years). These prescriptions were almost all for levonorgestrel ethinylestradiol (G03AA07; 76.8%). Only 1% of the males collected drugs for the genito urinary system and sex hormones.

The percentage of females collecting at least one prescription was significantly higher than males for nearly all medicine groups, except for the respiratory system, nervous system and systemic hormonal preparations, excluding sex hormones and insulins (***Table 2***). There was no significant difference between the percentage of males and females collecting at least one prescription for sensory organs (p=0.83).

Table 1. The most collected prescriptions per Anatomical Therapeutic Chemical (ATC) group, sorted from most to least, with the most relevant prescriptions per group

	ATC	Prescriptions (N=539,096)	
		n	%
Nervous system	**N**	**136,085**	**25.2**
Methylphenidate	N06BA04	72,077	13.4
Atomoxetine	N06BA09	3,657	0.7
Risperidone	N05AX08	8,184	1.5
Melatonin	N05CH01	14,620	2.7
Aripiprazole	N05AX12	3,322	0.6
Respiratory system	**R**	**105,508**	**19.6**
Desloratadine	R06AX27	17,739	3.3
Levocetirizine	R06AE09	8,936	1.7
Salbutamol	R03AC02	16,741	3.1
Fluticasone (glucocorticoids, inhalants)	R03BA05	8,143	1.5
Fluticasone (corticosteroids, topical use, nasal)	R01AD08	7,473	1.4
Dermatologicals	**D**	**89,003**	**16.5**
Other emollients and protectives	D02AX	11,054	2.1
Fusidic acid	D06AX01	7,104	1.3
Triamcinolone	D07AB09	6,501	1.2
Hydrocortisone	D07AA02	5,379	1.0
Erythromycin	D10AF02	5,307	1.0
Genito urinary system and sex hormones	**G**	**53,474**	**9.9**
Levonorgestrel and ethinylestradiol	G03AA07	38,767	7.2
Alimentary tract and metabolism	**A**	**52,232**	**9.7**
Sodium fluoride	A01AA01	11,334	2.1
Macrogol, combinations	A06AD65	6,414	1.2
Macrogol	A06AD15	4,087	0.8
Colecalciferol	A11CC05	4,574	0.8
Omeprazole	A02BC01	3,620	0.7
Anti-infectives for systemic use	**J**	**37,837**	**7.0**
Amoxicillin	J01CA04	6,631	1.2
Amoxicillin and beta-lactamase inhibitor	J01CR02	3,889	0.7
Nitrofurantoin	J01XE01	4,512	0.8
Doxycycline	J01AA02	4,267	0.8
Azithromycin	J01FA10	3,493	0.6
Sensory organs	**S**	**23,066**	**4.3**
Levocabastine	S01GX02	5,282	1.0
Musculoskeletal system	**M**	**17,656**	**3.3**
Diclofenac	M01AB05	6,751	1.3
Ibuprofen	M01AE01	5,226	1.0
Naproxen	M01AE02	3,912	0.7
Systemic hormonal preparations, excl. sex hormones and insulins	**H**	**8,584**	**1.6**
Levothyroxine sodium	H03AA01	2,836	0.5
Desmopressin	H01BA02	1,848	0.3
Prednisolone	H02AB06	1,665	0.3
Cardiovascular system	**C**	**5,019**	**0.9**
Propranolol	C07AA05	1,226	0.2
Blood and blood-forming organs	**B**	**4,970**	**0.9**
Ferrous fumarate	B03AA02	1,925	0.4
Antiparasitic products, insecticides and repellents	**P**	**3,463**	**0.6**
Antineoplastic and immunomodulating agents	**L**	**2,199**	**0.4**

Table 2. Prevalence rates (sorted from most to least) and number of prescriptions per person per Anatomical Therapeutic Chemical (ATC) (sub)group

	Users[a] (N=47,421)		No. of prescriptions per person		Users per gender[a]				p-value
ATC (sub)group	n	%	Median	IQR	Females (N=24,251) n	%	Males (N=23,170) n	%	
D Dermatologicals	**23,396**	**49.3**	**2**	**3**	**12,691**	**52.3**	**10,705**	**46.2**	**0.000***
Corticosteroids, dermatological preparations (D07)	11,195	23.6	1	1	6,239	25.7	4,956	21.4	0.000*
Emollients and protectives (D02)	6,559	13.8	1	1	3,682	15.2	2,877	12.4	0.000*
Anti-acne preparations (D10)	5,217	11.0	2	4	3,032	12.5	2,185	9.4	0.000*
R Respiratory system	**19,810**	**41.8**	**2**	**5**	**9,762**	**40.3**	**10,048**	**43.4**	**0.000***
Antihistamines for systemic use (R06)	9,863	20.8	2	3	4,804	19.8	5,059	21.8	0.000*
Drugs for obstructive airway diseases (R03)	6,349	13.4	3	5	3,006	12.4	3,343	14.4	0.000*
J Anti-infectives for systemic use	**16,753**	**35.3**	**1**	**1**	**9,493**	**39.1**	**7,260**	**31.3**	**0.000***
Antibacterials for systemic use (J01)	15,565	32.8	1	1	8,842	36.5	6,723	29.0	0.000*
A Alimentary tract and metabolism	**15,446**	**32.6**	**2**	**2**	**8,601**	**35.5**	**6,845**	**29.5**	**0.000***
Stomatological preparations (A01)	7,431	15.7	1	1	3,915	16.1	3,516	15.2	0.004*
Laxatives (A06)	4,572	9.6	2	2	2,805	11.6	1,767	7.6	0.000*
N Nervous system	**11,639**	**24.5**	**3**	**12**	**5,207**	**21.5**	**6,432**	**27.8**	**0.000***
Psychoanaleptics (N06)	5,500	11.6	9	16	1,726	7.1	3,774	16.3	0.000*
Psycholeptics (N05)	3,927	8.3	3	8	1,719	7.1	2,208	9.5	0.000*
G Genito urinary system and sex hormones	**10,952**	**23.1**	**4**	**5**	**10,742**	**44.3**	**210**	**0.9**	**0.000***
Sex hormones and modulators of the genital system (G03)	10,509	22.2	4	5	10,428	43.0	81	0.4	0.000*
S Sensory organs	**9,794**	**20.7**	**1**	**1**	**4,999**	**20.6**	**4,795**	**20.7**	**0.827**
Ophthalmologicals (S01)	6,806	14.4	1	1	3,479	14.4	3,327	14.4	0.967
M Musculoskeletal system	**9,226**	**19.5**	**1**	**1**	**5,618**	**23.2**	**3,608**	**15.6**	**0.000***
Anti-inflammatory and antirheumatic products (M01)	9,091	19.2	1	1	5,561	22.9	3,530	15.2	0.000*
P Antiparasitic products, insecticides and repellents	**2,566**	**5.4**	**1**	**0**	**1,417**	**5.8**	**1,149**	**5.0**	**0.000***
Antiprotozoals (P01)	1,452	3.1	1	0	869	3.6	583	2.5	0.000*
H Systemic hormonal preparations, excl. sex hormones and insulins	**1,835**	**3.9**	**2**	**3**	**877**	**3.6**	**958**	**4.1**	**0.003***
Corticosteroids for systemic use (H02)	967	2.0	1	1	506	2.1	461	2.0	0.456
B Blood and blood-forming organs	**1,630**	**3.4**	**2**	**2**	**1,151**	**4.8**	**479**	**2.1**	**0.000***
Antianemic preparations (B03)	1,213	2.6	2	2	915	3.8	298	1.3	0.000*
C Cardiovascular system	**1,382**	**2.9**	**1**	**2**	**795**	**3.3**	**587**	**2.5**	**0.000***
Beta blocking agents (C07)	620	1.3	1	2	409	1.7	211	0.9	0.000*
L Antineoplastic and immunomodulating agents	**245**	**0.5**	**4**	**10**	**141**	**0.6**	**104**	**0.5**	**0.044***
Immunosuppressants (L04)	140	0.3	7	11	79	0.3	61	0.3	0.210

* $p<0.05$.

[a] User was defined as an adolescent who collected at least one prescription within the ATC (sub)group.

Excl, excluding; IQR, interquartile range; No, number.

Figure 1 shows the percentage of males and females collecting at least one prescription within the ATC groups (prevalence) per age. The percentage of adolescents collecting drugs for the alimentary tract and metabolism (A), nervous system (N), respiratory system (R), and sensory organs (S) decreased during adolescence, whereas adolescents collecting prescriptions for anti-infectives for systemic use (J) and drugs for the cardiovascular system (C) and musculoskeletal system (M) increased over time (nervous system p=0.02; others p=0.00). The male users of dermatologicals (D) slightly increased, whereas the percentage of females users decreased during adolescence (p=0.00; ***Figure 1***). Some user percentages did not change over time, such as females using systemic hormonal preparations, excluding sex hormones and insulins (H; p=0.26) and antiparasitic products, insecticides and repellents (P; p=0.14). For males, the percentage using blood and blood-forming organs (B) stayed the same (p=0.69). For both genders, the use of antineoplastic and immunomodulating agents (L) did not change over time (p=0.19 males; p=0.14 females).

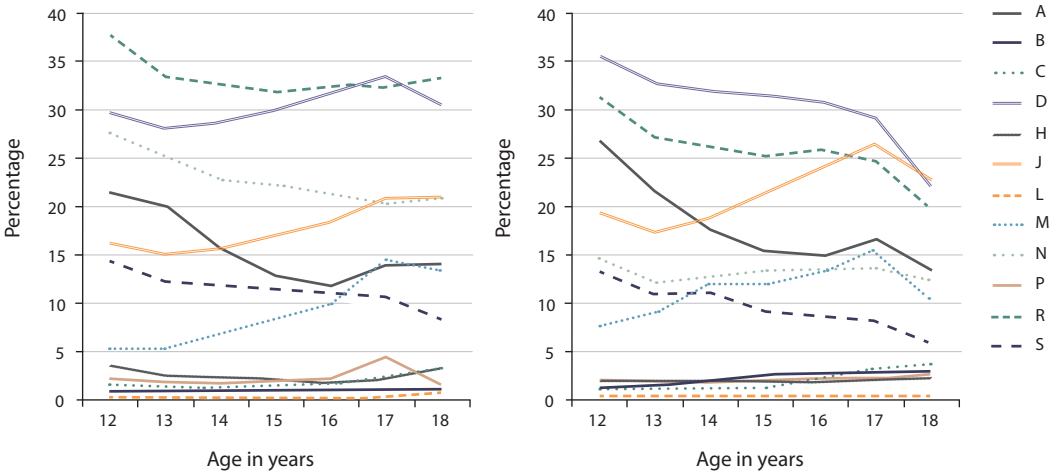

Figure 1. Percentage of males (left) and females (right) collecting one or more prescriptions within the anatomical main group over the years. Prescriptions for 'genito urinary system and sex hormones' are not shown, as those were mostly contraceptives.

A, alimentary tract and metabolism; B, blood and blood-forming organs; C, cardiovascular system; D, dermatologicals; H, systemic hormonal preparations, excl. sex hormones and insulins; J, anti-infectives for systemic use; L, antineoplastic and immunomodulating agents; M, musculoskeletal system; N, nervous system; P, antiparasitic products, insecticides and repellents; R, respiratory system; S, sensory organs.

DISCUSSION

We provided a comprehensive overview of drug utilisation in adolescents, showing that most adolescents collected at least one prescription for dermatologicals, drugs for the respiratory system or anti-infectives for systemic use. Our data suggest that eczema/acne, allergic rhinitis/asthma and

systemic infections are most common among adolescent medication users. The highest number of collected prescriptions was for methylphenidate, while levonorgestrel ethinylestradiol was mostly collected among adolescent females.

A previous study using integrated primary care information (i.e. medical records from the period 2000 - 2005) showed similar results. However, this study showed the highest prevalence rate for anti-infectives. Levonorgestrel was the most used drug, and drugs for the nervous system were less commonly used compared with our results.[8] In our study, we used pharmacy prescription records, which provides a reliable overview of drugs that are actually collected by the patient. In addition, the use of methylphenidate increased the last years, which might explain the difference.[9] Another study, focusing on 15-year-old adolescents, reported that anti-inflammatory drugs, analgesics and systemic antihistamines were mostly used.[4,10] However, these results were based on self-reported use for a period of four weeks, while the average follow-up time in our study was almost three years.

The current study results are based on a large sample (N=47,421) and therefore provides a valuable and updated overview of drug utilisation among adolescents compared with previous studies. Our database contained prescription data from all adolescents registered at 62 community pharmacies, which is roughly 3% out of 1,994 community pharmacies operating in the Netherlands in 2017.[11] Dutch patients are generally registered at a single community pharmacy and usually fills all their prescriptions in this pharmacy. Pharmacy prescription records give therefore a complete medication overview and there is no desirability bias, as results are not based on self-report. However, our results might be an overestimation of drug use, because collecting a prescription does not necessarily mean using the drug.[12]

A limitation is the lack of indication for use, which is not included in pharmacy prescription records. However, drug use may be a good indicator for the underlying disease.

The aim of this short report was to provide a comprehensive and updated overview of drug use among adolescents. Most adolescents collected at least one prescription for dermatologicals, drugs for the respiratory system, and anti-infectives for systemic use. Future research should focus on adolescents who collect most prescriptions to create a better understanding of adolescent healthcare use and their needs.

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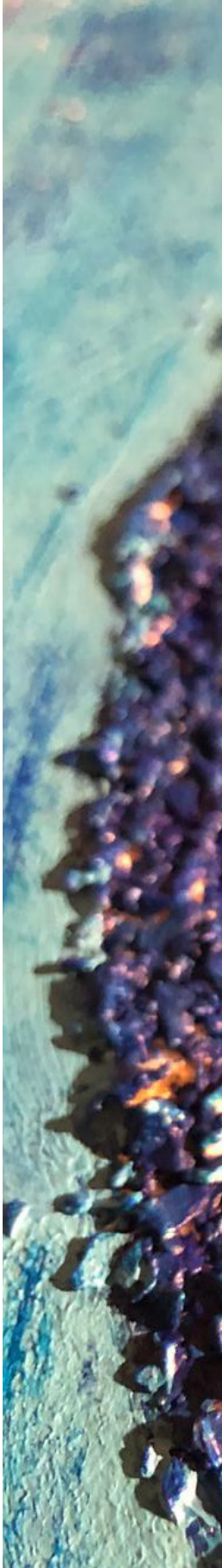

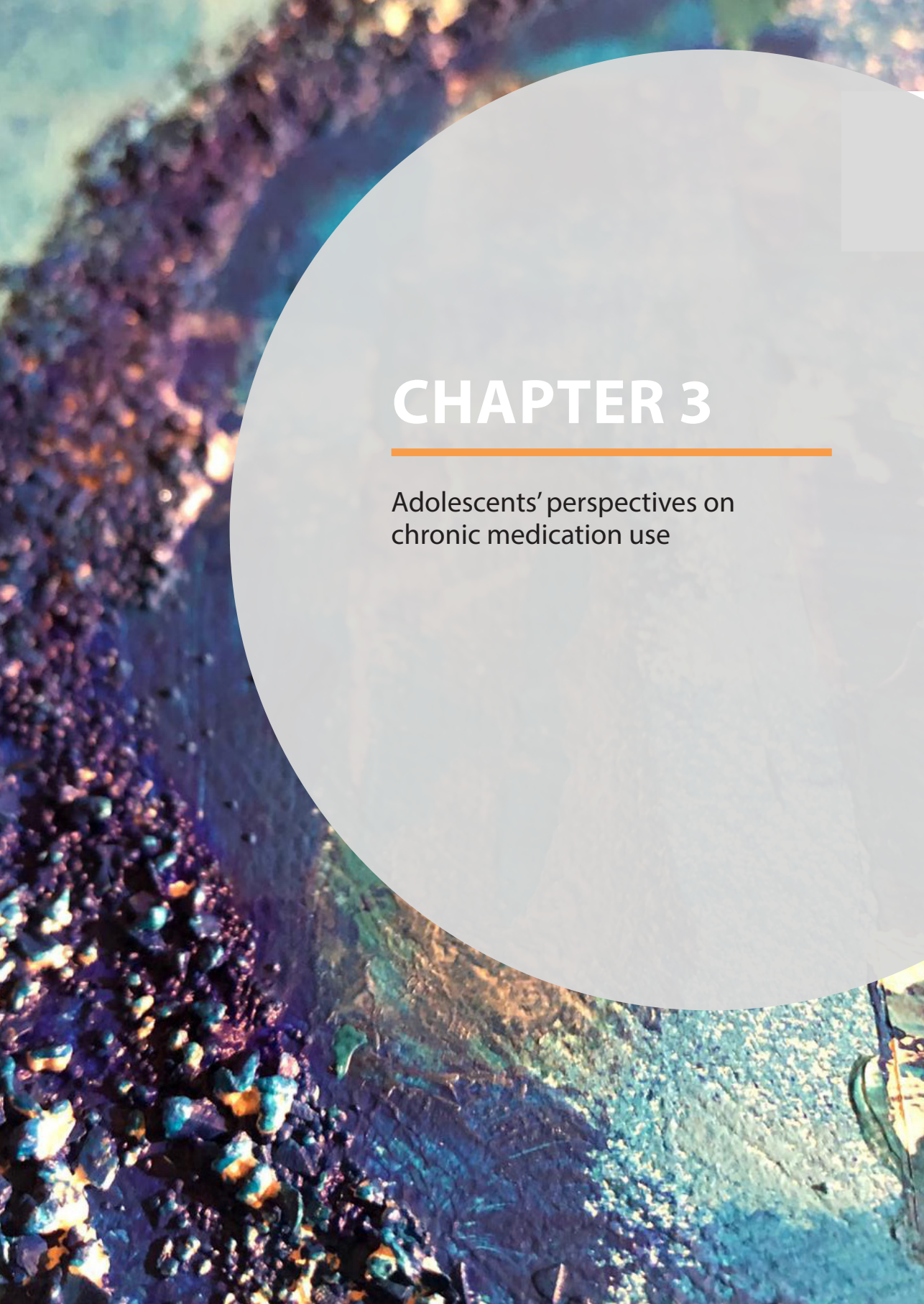

CHAPTER 3

Adolescents' perspectives on chronic medication use

CHAPTER 3.1

Adolescents' perspectives on atopic dermatitis treatment - experiences, preferences, and beliefs

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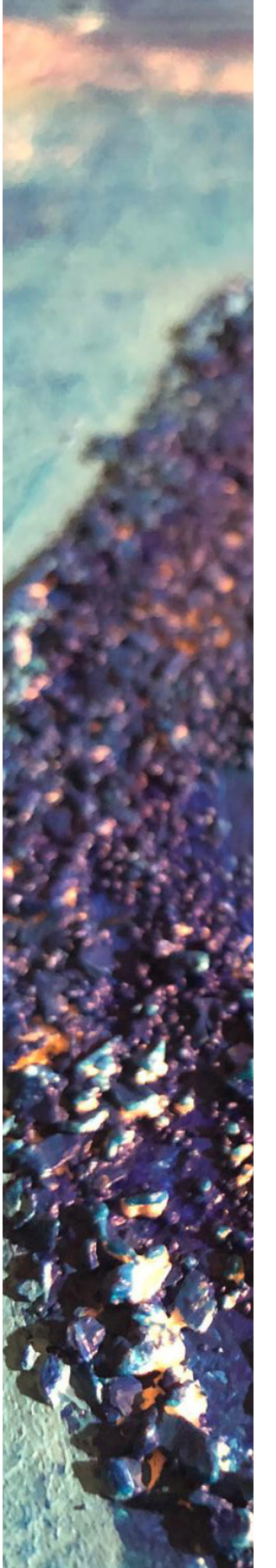

ABSTRACT

Importance: For a considerable proportion of paediatric patients, atopic dermatitis symptoms persist into adolescence. Previous studies have focused mainly on (parents of) children, whereas little is known about adolescents with atopic dermatitis.

Objective: To explore the beliefs, experiences, and preferences of adolescents with atopic dermatitis towards their treatment.

Design, setting, and participants: We conducted a qualitative study employing focus group interviews of 15 adolescents (age 12 - 18 years) who collected at least one prescription for topical corticosteroids in class 2 (moderately potent) or 3 (potent) in the preceding year. The study included nine community pharmacies in three different regions in the Netherlands. Data were collected from November to December 2016, until data saturation was reached. Focus groups were recorded, transcribed verbatim, and data were analysed by two researchers.

Main outcomes and measures: Adolescents' beliefs, experiences, and preferences toward their atopic dermatitis treatment were explored during focus groups. We used a thick analysis approach to analyse the transcripts; both deductive and inductive coding were used to analyse the transcripts.

Results: Three focus groups including 15 adolescents (8 males) with a mean age of 15.3 years (range 12 - 18 years) were conducted. Adolescents were in general satisfied with the efficacy of the treatment; however, they prefer a faster and more persistent effect. Most adolescents had little contact with their physicians and did not completely adhere to the prescribed medication regimen; they developed their own routine of using topical corticosteroids in combination with emollients and moisturizers. They also seemed to have incorrect beliefs about the mechanism of action.

Conclusions and relevance: Adolescents developed their own way of using topical treatment for atopic dermatitis. Some practical suggestions were mentioned to improve medication use. Healthcare providers should devote special attention to adolescents with atopic dermatitis to make them more aware of the principles of topical treatment and ensure proper use.

INTRODUCTION

For approximately 20% of paediatric patients with atopic dermatitis, symptoms persist into adolescence.[1] Appropriate use of emollients, moisturizers, and topical corticosteroids (TCS) is of utmost importance to reach sufficient disease control.[2] However, TCS adherence rates are generally low (e.g. owing to corticophobia).[3-6] During adolescence, many physical, social, and psychological changes occur, and body image plays a more important role. Having atopic dermatitis during this period may considerably affect quality of life.[7] However, studies involving adolescents with atopic dermatitis are scarce.[2,8] We therefore aimed to explore the beliefs, experiences, and preferences of adolescents with atopic dermatitis towards their treatment.

METHODS

We organised focus groups (November and December 2016), including four to six adolescents per group, until data saturation was reached. We selected adolescents (age 12 - 18 years) with atopic dermatitis in nine community pharmacies. Adolescents were selected from the pharmacy information system based on medication filling: adolescents who filled at least one prescription of TCS in class 2 (moderately potent, D07AB) or 3 (potent, D07AC) in the preceding year were invited.[9] All participants (and parents when younger than 16 years) provided written informed consent. Before the start of the focus groups, information on patient characteristics, such as age, sex, country of origin, and educational level were collected.

During the focus groups, four main topics were discussed: (1) impact on daily life, (2) medication use, (3) information provision, and (4) suggestions to improve treatment. The focus groups were audiotaped and the recordings were transcribed verbatim. A thick analysis approach was used to analyse the data; a codebook with thematic codes was developed beforehand and applied to all transcripts (deductive coding). Second, open codes were created and subsequently applied to all transcripts (inductive coding).[10] Summaries were made per participant, and a combination of analytical techniques (searching and finding) and tactics (connecting) was used to obtain a comprehensive overview of the main themes.

All personal data was encrypted using a study code, ensuring privacy of all participants. The study was approved by the institutional review board of the Utrecht Pharmacy Practice network for Education and Research (UPPER), Department of Pharmaceutical Sciences, Utrecht University. Data analyses were performed using ATLAS.ti (version 7.5.17, Scientific Software Development).

RESULTS

Three focus groups (duration between 75 and 85 minutes) were held, including 15 adolescents (mean age 15.3 years; range 12 - 18 years) (***Table 1***). Most frequently mentioned issues are shown in ***Figure 1***, and quotes per focus group topic are shown in ***Table 2***. Most adolescents had a neutral or indifferent attitude, whereas adolescents with severe atopic dermatitis often had a more negative attitude towards their disease.

Table 1. Characteristics of the 15 participants in the study

	n (%)
Age, mean (range), y	**15.3 (12 - 18)**
Male gender	**8 (53.3)**
Native Dutch origin	**14 (93.3)**
Education	
High school: vocational level	9 (60.0)
High school: pre-university level	5 (33.3)
University	1 (6.7)
Onset atopic dermatitis	
At birth	7 (46.7)
Childhood (8-11 y)	3 (20.0)
Adolescence (12-14 y)	5 (33.3)
Affected area atopic dermatitis[a]	
Upper limbs	11 (73.3)
Lower limbs	8 (53.3)
Head and neck	7 (46.7)
Anterior trunk	4 (26.7)
Back	4 (26.7)
Topical corticosteroids used[b]	
Moderately potent (D07AB)	9 (60.0)
Potent (D07AC)	8 (53.3)
Very potent (D07AD)	2 (13.3)

[a] Adolescents could have more than one affected area.

[b] Adolescents could use more than one type of corticosteroids.

Itch and pain were commonly mentioned and almost all participants experienced worsening of symptoms after showering and physical exercise with sweating as a result. Few adolescents received negative comments or questions from peers and some adolescents adjusted their clothing to their symptoms, e.g. wearing long trousers to cover the affected skin. Nonetheless, having atopic dermatitis did not interfere with daily activities of most participants.

Adolescents were in general satisfied with the efficacy of the treatment, however they prefered a faster and more persistent effect. Almost all adolescents developed their own routine in using topical treatment, which often deviates from the proposed medication regimen by the physician. In general, they used TCS more and longer than prescribed; half of the adolescents used TCS every day and did not (always) use emollients or moisturizers on a daily basis. Some of the patients with abundant TCS use reported thinner skin as a side effect, however they continued using it. The main reason for everyday use was the (lack of) efficacy when using less. Limited time, forgetting, and indifference were also mentioned as factors for aberrant use. In our study, the adolescents had a lack of knowledge about the treatment and incorrect beliefs about the mechanism of action. Negative experiences with the treatment were stickiness, bad odor, and itchy/burning feeling. The application of topical treatment was not time consuming, ranging from a few to 10 minutes; however, adolescents mentioned that the dermal absorption was slow and did not always fit with their busy schedules, e.g. rushing in the morning to get to school.

Most adolescents had little contact with their physician and the advice on how to use TCS (in combination with emollients or moisturizers) differed between clinicians; general practitioner, dermatologist, and pharmacist. Some adolescents (with less severe symptoms) visited a physician only once and received repeat prescriptions without a physician visit, whereas others regularly visited their dermatologist or general practitioner. Most adolescents forgot the information they received at the start of treatment; however, at the time of the focus group they did not feel a need for additional information.

Mainly practical issues were mentioned as suggestion to improve treatment: a faster dermal absorption; oral treatment; test samples; a demonstration on how to use TCS at the start of treatment; follow-up visits with the physician, in particular at start of treatment; shorter (digital) information leaflet; other packaging (jar or plastic tube); and (online) contact with peers was preferred during early adolescence.

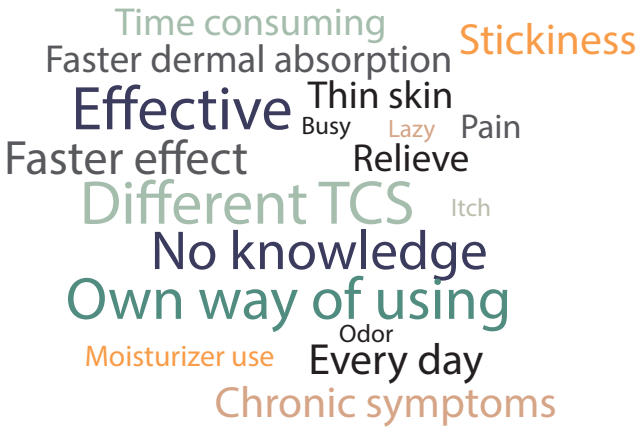

Figure 1. Word cloud with the most frequently mentioned issues by adolescents treated for atopic dermatitis.
TCS, topical corticosteroids.

Table 2. Overview of adolescents' quotes per topic

Topic	Adolescent, Sex (Age, y)	Quote
Impact on daily life	Male (16)	"It's just normal to me… I'm used to it. Having atopic dermatitis does not make me differ from other adolescents."
	Female (16)	"At school it is sometimes hard to hold a pen, due to the affected skin on my hand it is hard to move my fingers."
Medication use	Male (17)	"The only thing I know is that you should not use it too often."
	Male (15)	"The symptoms do not totally disappear... I know that that's not possible, they will always return, but a faster effect would be great."
	Female (12)	"Sometimes it´s annoying, especially in the morning, because greasy spots appear in my trouser due to the creams."
	Male (17)	"The label stated 'apply three times per day', but I only use it when I have symptoms."
	Female (16)	"If I apply the cream, it takes ages before it is absorbed."
Information provision	Female (12)	"I have been using topical corticosteroids for a long time, so I don't remember what they told me the first time."
	Female (14)	"At the moment, I don't need information about the application of creams, but it would have been useful at the start of treatment."
	Male (13)	"It would be good if they showed you how to apply the cream, when collecting it for the first time."
Suggestions to improve treatment	Female (14)	"A follow-up visit would have been great. Just to share experiences and to adjust treatment when needed. It will also help healthcare providers to improve themselves."
	Male (18)	"Currently I do not need it, but when one is younger it might be nice to share experiences with peers and receive advice from older children."

DISCUSSION

Our study showed that most adolescents with atopic dermatitis had a neutral or indifferent attitude towards their disease. They developed their own routine of using TCS, emollients, and moisturizers, and they were in general satisfied with the result. This does not always imply that

their self-management routines are the preferred routine from a physician's perspective. However, adolescents received various instructions on the application of topical treatments from different clinicians. Adolescents suggested mainly practical treatment improvements, such as a faster dermal absorption, a persistent and faster effect, and packaging suggestions.

The treatment of atopic dermatitis is complex because TCS should be alternately used with emollients and moisturizers, and they all have a different regimen. A recently published review emphasized that TCS are more effective in combination with emollients or moisturizers.[2] This emphasizes the importance of a clear explanation (and demonstration) of the treatment. Adolescents in our study also suggested this, and there is room to improve the knowledge of adolescents with atopic dermatitis, i.e. the principle of the topical treatment was for most adolescents unclear and they had incorrect beliefs about the mechanism of action.

Limitations

Qualitative sampling is a suitable way to collect exploration data, however it has some limitations, for example the possibility of a response bias. These results might therefore not be generalizable to all adolescents with atopic dermatitis. Yet, our study population was a representative adolescent sample based on age, sex, and education level. Moreover, there was a broad heterogeneity in disease severity among the participants and all focus groups contained adolescents in a wide age range, which increases external validity.

CONCLUSIONS

The current study shows that adolescents developed their own way of using topical treatment for atopic dermatitis. Some practical suggestions were mentioned to improve medication use. Healthcare providers should devote special attention to the treatment of adolescents with atopic dermatitis to make them more aware of the principles of topical treatment and ensure correct use.

ACKNOWLEDGEMENTS

The authors thank the adolescents who participated in the focus groups for their valuable input.

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CHAPTER 3.2

Attention-deficit/hyperactivity disorder medication use in adolescents: the patient's perspective

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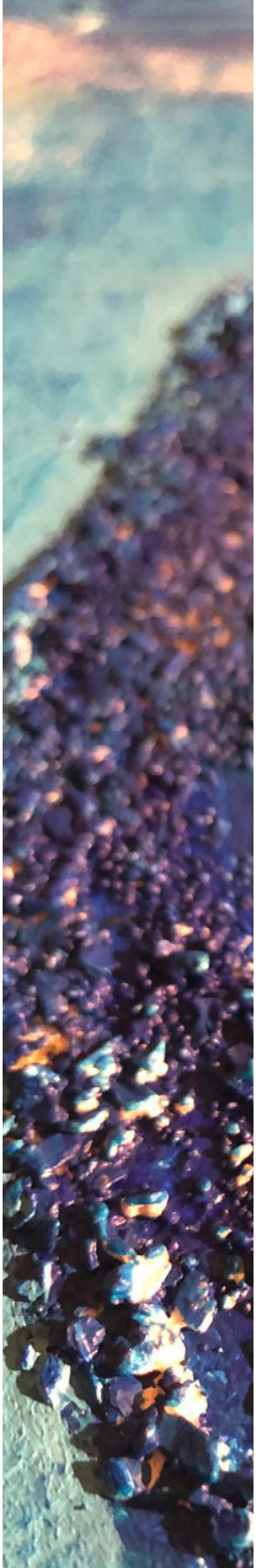

ABSTRACT

Purpose: The purpose of the study was to gain more insight into the attitudes of adolescents using medication for attention-deficit/hyperactivity disorder (ADHD).

Methods: A cross-sectional study among adolescents (age 12 - 18 years) who filled at least two prescriptions for ADHD medication in the preceding year was conducted. Adolescents were invited to fill in an online questionnaire containing questions on sociodemographics, health status, illness perceptions, medication adherence, and medication beliefs.

Results: We invited 1,200 adolescents of whom 181 adolescents (122 males, mean age 14.2 ± 1.7 years) completed the online questionnaire. They mostly used methylphenidate (n=167; 92%) as a pharmacological treatment for ADHD. Half of the study population (n=93; 51%) experienced side effects, such as decreased appetite and sleep problems. Most participants (n=150; 83%) had an indifferent attitude (perceived low necessity and low concerns) toward their ADHD medication. More than half of the study population (n=111; 61%) reported to be non-adherent based on the Medication Adherence Report Scale. The highest score of the Brief Illness Perception Questionnaire was on 'treatment control', suggesting that adolescents do think their medication is effective, despite their indifferent drug attitude.

Conclusions: Most adolescents using ADHD medication had an indifferent attitude toward their medication and reported low adherence rates. These findings should be taken into account when treating adolescents with ADHD; regular counseling and monitoring of the pharmacological treatment might be useful to optimize treatment.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a neuropsychiatric disorder characterized by having a short attention span, easily being distracted, excessive activity, or difficulties with controlling behaviour, which is not appropriate for a person's age. This results in suboptimal performances in social, educational, or work settings.[1] The highest prevalence of ADHD is found in children and adolescents; approximately 63 million children and adolescents are diagnosed with ADHD worldwide.[2]

Adolescence is a distinctive life phase which is characterized by psychological, physical, and emotional changes. During transition from childhood to adolescence, there is a shift in ADHD symptoms and behaviour from hyperactivity and impulsivity to more antisocial behaviour.[3] Substance misuse and lower educational performance are often observed in adolescents with ADHD. They also display higher rates of oppositional defiant disorder, anxiety, depression, and they report a lower quality of life compared with their unaffected peers.[3-5]

In addition to behavioural therapy, pharmacotherapy is used to control ADHD symptoms, that is, reduce hyperactivity and increase focus. The pharmacological options in the Netherlands are stimulants (methylphenidate and amphetamines) and nonstimulants (e.g. atomoxetine).[6] Currently, the number of medication users is increasing with 12,000 each year, with approximately 215,000 users in 2015.[7] Methylphenidate is the most commonly prescribed ADHD treatment worldwide, and it improves teacher-reported ADHD symptoms and behaviour. Parents even reported an increased quality of life among younger children. However, the use of methylphenidate is also associated with adverse effects.[8,9] Several studies have shown that a substantial proportion of ADHD patients discontinue medication or are poorly adherent; non-adherence rates of children and adolescents using ADHD medication vary between 10% and 64%.[10]

Adolescents undergo psychosocial changes and they start to develop their own attitudes and beliefs, which may affect their medication use and adherence levels.[11-13] Therefore, adolescence is an important life phase for medication intake behaviour. However, most previous research has focused on attitudes and beliefs of parents and teachers towards ADHD medication, focused on younger children, or take children and adolescents together as one group,[9,13-15] while the highest use of methylphenidate is during adolescence (age 14 years).[16]

Some studies have been done regarding the beliefs of adolescents about the disorder ADHD, while the specific beliefs of adolescents regarding ADHD medication have not yet been studied. There are also some doubts about the effectiveness of pharmacological treatments, and the adolescents' opinion might be important to improve this.[9,13] The aim of our study was to gain more insight into adolescents' actual use of ADHD medication and their attitudes towards medication use and disease.

METHODS

Study design and setting

A cross-sectional study among adolescents using ADHD medication was conducted. Adolescents were selected from community pharmacies affiliated with the Utrecht Pharmacy Practice Network for Education and Research (UPPER). This network contains over 1,300 community pharmacies and provides internship and research opportunities.[17] In April 2015, all community pharmacies in the network received an e-mail to participate in the study.

Participants

Adolescents (age 12 - 18 years) were selected from the pharmacy information system in the participating pharmacies based on filling of at least two prescriptions for methylphenidate (Anatomical Therapeutic Chemical Classification System N06BA04),[18] dexamphetamine (N06BA02), and/or atomoxetine (N06BA09) in the preceding year. Adolescents who filled these criteria received a postal letter with a link to an online questionnaire.

Data collection

The online questionnaire consisted of sociodemographic questions (age, gender, educational level, and ethnicity), a health status question, medication-related questions (type, duration of use, and side effects), and questions about the role of parents and friends. It also contained validated questionnaires on self-reported adherence (Medication Adherence Report Scale [MARS]),[19] beliefs about medicines (Beliefs about Medicines Questionnaire-specific [BMQ-specific]),[20] and illness perceptions (Brief Illness Perception Questionnaire [Brief-IPQ]).[21] The focus of the online questionnaire was on ADHD medication use, which was clearly stated in the introduction and above every part of the questionnaire.

Outcomes: adherence, medication beliefs, and illness perceptions

The *MARS* was used to assess self-reported adherence. This questionnaire consists of five questions covering both intentional and unintentional non-adherence. All items were scored on a five-point Likert scale ranging from 1 (always) to 5 (never) resulting in a total score between 5 and 25, where a higher MARS score indicates higher self-reported adherence.[19,22] MARS scores were dichotomized by using a cut-off point of ≥23 for sufficiently adherent, based on previous studies.[23,24] The online questionnaire included three additional multiple choice (with 'other option') questions on medication use to assess (reasons for) non-adherence and to get an insight into medication use during weekends or holidays.

The *BMQ-specific* was used to assess adolescents' beliefs about the necessity of their ADHD medication and their concerns about potential adverse consequences of taking ADHD medication. The questionnaire consists of 10 items divided over two subscales; five items on necessity (e.g. my life would be impossible without my medicines) and five items on concerns (e.g. having to take

medicines worries me). All items were scored on a five-point Likert scale (strongly disagree to strongly agree), resulting in a score of 5 to 25 for each scale. A higher score indicates a stronger belief in the concepts represented by the subscale.[20] Scores above the scale midpoint (score >15) were considered as strong beliefs, resulting in four attitudinal groups: accepting (high necessity, low concerns), ambivalent (high necessity, high concerns), indifferent (low necessity, low concerns), and sceptical (low necessity, high concerns).[25]

The *Brief-IPQ* was used to assess adolescents' illness perceptions. This questionnaire measures cognitive and emotional representation of their illness and it covers nine different dimensions: consequences, timeline, personal control, treatment control, identity, coherence, emotional representation, concerns, and causes. The causes item was excluded, because this open-ended item was perceived as complicated by young adolescents in a previous study. The remaining eight dimensions were measured on a 0 (not at all) to 10 (very much) response scale.[21]

Ethics and confidentiality

Before start of the study, approval was obtained from the institutional review board of the division of Pharmacoepidemiology and Clinical Pharmacology, Department of Pharmaceutical Sciences, Utrecht University. The first page of the online questionnaire contained an informed consent form. Adolescents aged <16 years additionally had to ask their parents to agree with participation. Data were collected anonymously, since adolescents were only asked about their gender and date of birth, and questionnaire data could not be linked to patient data in the community pharmacies.

Data analysis

Descriptive statistics were calculated. For skewed data, the median with interquartile range (IQR) is shown instead of the mean with standard deviation. The Kruskal-Wallis test was used to test for adherence differences between the four attitudinal groups. Sensitivity analyses were performed using different cut-offs for adherence based on MARS scores (≥21 and 25). Statistical analyses were performed using IBM SPSS Statistics for Windows (version 23.0). P-values <0.05 were considered statistically significant.

RESULTS

Study population

In total, 68 pharmacies participated in the study. Approximately 1,200 adolescents were invited and 235 adolescents opened the link to the online questionnaire. Of those, 183 adolescents completed the questionnaire. Two adolescents had to be excluded because their parents filled out the questionnaire. Therefore, the final study population consisted of 181 adolescent users of ADHD medication (***Figure 1***). Characteristics of the study population are shown in ***Table 1***: 66.9% males, mean age 14.2 ± 1.7 years (median 14; IQR 2), the majority (98.3%) was of native Dutch origin and

51.9% was enrolled in a pre-university high school. Most adolescents (95.6%) reported a (very) good or excellent health status.

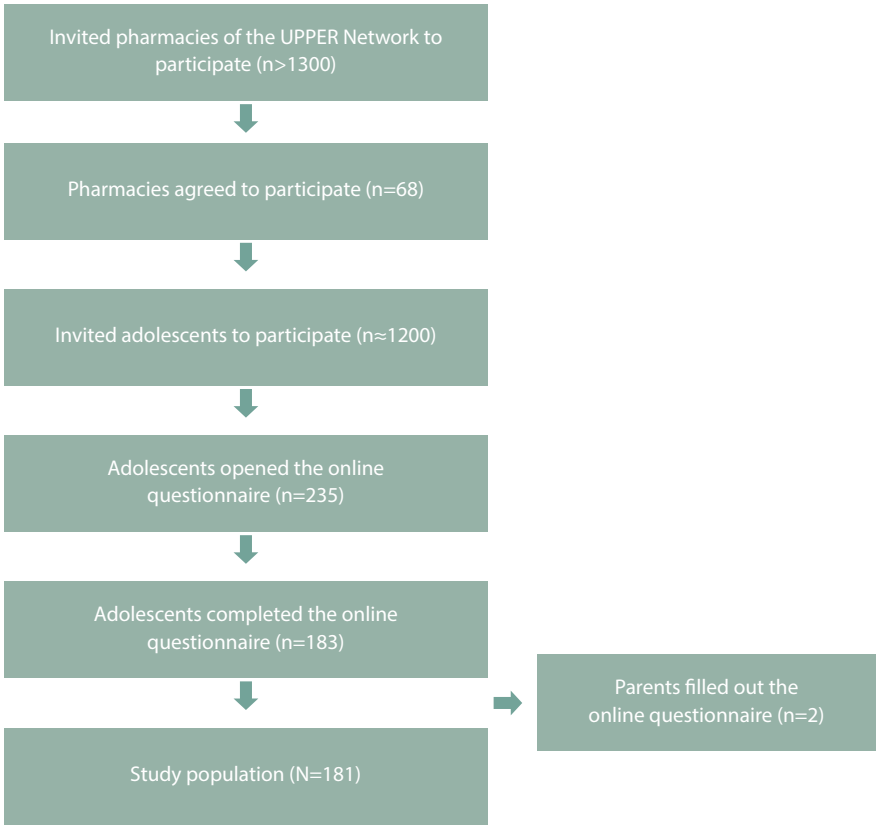

Figure 1. Flow chart of the study procedure and study population.
UPPER, Utrecht Pharmacy Practice network for Education and Research.

Medication use

Methylphenidate was the most frequently used ADHD medication. The mean age at which adolescents said they started ADHD medication was 10.7 years (***Table 1***). Most important reasons for medication use were to increase focus, treat ADHD symptoms, and achieve better school results. Half of the participants (51.4%) reported side effects, in particular decreased appetite and sleep problems. Only a few adolescents (5.5%) gave (at least once) some of their medication to friends, family, or classmates.

Table 1. Characteristics of the study population (N=181)

	% (n)
Male gender	**66.9 (121)**
Age, mean (SD)	**14.2 (1.7)**
Native Dutch origin	**98.3 (178)**
Education	
Elementary school	9.4 (17)
High school: vocational level	34.8 (63)
High school: pre-university level	51.9 (94)
Other	3.9 (7)
Lifestyle	
Alcohol use	22.7 (41)
Tobacco use	10.5 (19)
Playing sport	74.6 (135)
Sport hours per week (mean, SD)	4.6 (2.9)
Self-reported health status	
Excellent	18.2 (33)
Very good	33.1 (60)
Good	44.2 (80)
Moderate	4.4 (8)
Medication type	
Methylphenidate	92.3 (167)
Dexamphetamine	3.9 (7)
Atomoxetine	1.1 (2)
Combination (methylphenidate and dexamphetamine/atomoxetine)	2.8 (5)
Duration, mean years (SD)	**3.5 (2.5)**
Side effects	**51.4 (93)**

SD, standard deviation.

Self-reported medication adherence

The median MARS score was 22 (IQR 4). More than half of the study population (61.3%; n=111) scored below the cut-off of 23 and are thereby defined as non-adherent. The median of the items related to intentional non-adherence (items 2 - 5) was 5, representing 'never', and the median of item 1 (unintentional non-adherence) was 4, representing 'rarely' (***Table 2***). The percentage of adolescents who scored 1 to 3 (always to sometimes) was the highest at items 1, 3 and 4: forgetting (27.6%), stopping for a while (28.2%), and deciding to miss out a dose (25.4%), ***Table 2***.

Almost half of the study population (48.1%) stated that they occasionally deviate from the prescribed dosing regimen, and 60.2% reported that they occasionally discontinue medication during weekends or holidays, that is, answered *"yes"* to the question: *"Do you sometimes decide not to take your medication during weekends or holidays?"*.

Table 2. The median and interquartile range (IQR) of the Medication Adherence Report Scale (MARS) score per item; score range 1 (always) to 5 (never). The last column represents the percentage of the population scoring 1 (always) to 3 (sometimes).

MARS items	Median (IQR)	Scoring 1-3 % (n)
1. I forget to take my medicines	4 (1)	27.6 (50)
2. I change the dosage of my medicines	5 (1)	13.3 (24)
3. I stop taking my medicines for a while	5 (2)	28.2 (51)
4. I decide to skip one of my medication dosages	5 (2)	25.4 (46)
5. I use my medication less than is prescribed	5 (1)	17.7 (32)

IQR, interquartile range; MARS, Medication Adherence Report Scale.

Beliefs about ADHD medication

The mean score on the BMQ-necessity scale was 11.0 ± 3.5 (range 5 - 23) and the mean score on the concerns scale was 9.7 ± 3.5 (range 5 - 19). The minority (11%) of the study population reported high necessity beliefs, and 7.2% reported high concerns about ADHD medication (scores above midpoint). More than half of the study population (61.9%) had a positive necessity-concern differential and there was a weak correlation (0.203) between this necessity-concerns differential and the MARS total score (p=0.006).

Most adolescents (83%) had low necessity beliefs and low concerns towards ADHD medication, a so-called indifferent attitude. The distribution over the other three drug attitudes was 10% accepting (high necessity, low concerns), 6% sceptical (low necessity, high concerns), and two adolescents (1%) were ambivalent (high necessity, high concerns). ***Figure 2*** showed the distribution of the study population over the four drug attitudes based on their BMQ-specific score, with the corresponding adherence rates based on their MARS score (≥23). Statistical analysis showed no significant difference (p=0.104) between the adherence rates of the four drug attitude groups. Sensitivity analyses were performed using different cut-offs (MARS scores ≥21 and 25); these did not affect the results (data not shown). There was also no significant difference (p=0.098) between adherence percentages of the four drug attitudes based on the question *"take medication sometimes differently than prescribed"*.

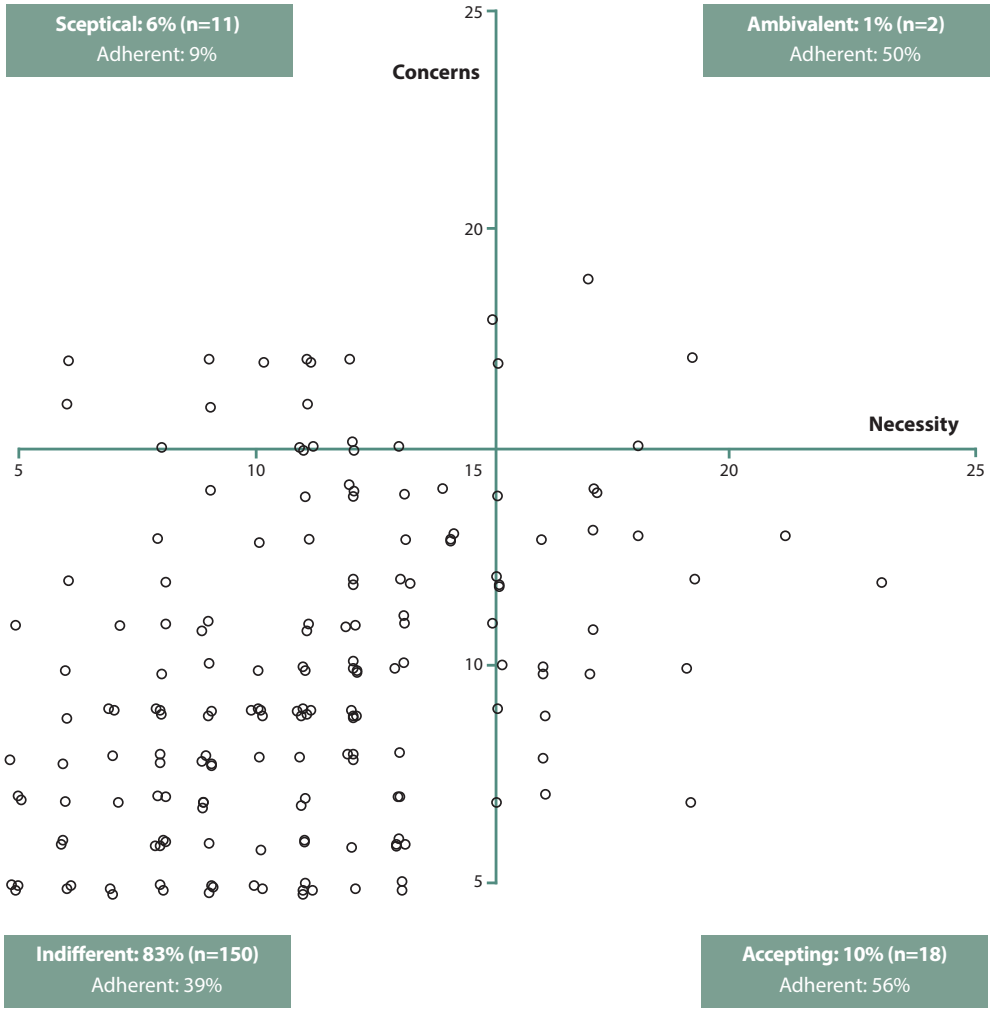

Figure 2. Scatter plot of the necessity and concern scores, divided in four drug attitude groups. Scores above scale midpoint (>15) were considered as strong beliefs. The percentage of adolescents with a particular attitude towards their medicines and their corresponding adherence rate (based on Medication Adherence Report Scale [MARS] ≥23) are shown. No significant difference (p=0.104) is found between the adherence rates of the four drug attitudes.

Adolescents' perception toward disease

The illness perception questionnaire (Brief-IPQ) was completed by 180 adolescents. ***Table 3*** shows the median and IQR per item. Adolescents scored the highest on treatment control (median 8, IQR 2) and coherence (median 8, IQR 4). The lowest scores were on identity (median 1, IQR 4) and illness concern (median 2, IQR 3).

Table 3. The median score and interquartile range (IQR) on the Brief Illness Perception Questionnaire (Brief-IPQ) items; response scale 0 (not at all) to 10 (very much)

Domain	Item	Question	Median (IQR)
Cognitive illness representations	Consequences	How much does your illness affect your life?	6 (2)
	Timeline	How long do you think your illness will continue?	7 (5)
	Personal control	How much control do you feel you have over your illness?	5 (3)
	Treatment control	How much do you think your medication can help your illness?	8 (2)
	Identity	How much do you experience symptoms from your illness?	1 (4)
Illness comprehensibility	Coherence	How well do you feel you understand your illness?	8 (4)
Emotional representations	Emotional representation	How much does your illness affect you emotionally? (e.g. does it make you angry, scared, upset or depressed?)	5 (5)
	Illness concern	How concerned are you about your illness?	2 (3)

IQR, interquartile range.

DISCUSSION

Most adolescents (83%) in this study had an indifferent drug attitude; they experience low necessity and have low concerns toward their ADHD medication. A similar attitude is observed in a study focusing on adolescents using inhaled corticosteroids.[23] Previous research showed necessity beliefs to be associated with adherence;[12,26,27] however, our study showed no significant difference in adherence between the four drug attitude groups. This might be related to the sample size and the distribution of adolescents over the drug attitudes. On the other hand, we showed a weak correlation between the differential 'necessity-concerns' and MARS total score, suggesting that higher perceived necessity is slightly associated with higher adherence rates.

The MARS scores suggest that less than 40% of the adolescents is adherent to their ADHD medication (MARS score ≥23). The lowest scores were found on the item related to unintentional non-adherence, suggesting that forgetting is a major reason for not taking medication as prescribed in adolescents

with ADHD. This is confirmed by the additional adherence questions, where 'forgetting' was selected as the most important reason for non-adherence. This is in line with results from studies in adolescents with asthma or inflammatory bowel disease.[28,29] Forgetting seems age specific, since adolescents are still in the process of developing their executive functions and self-regulation skills. Moreover, most adolescents have busy schedules and are forgetful about all, except items of their highest priority, such as their friends.

Another main reason for aberrant medication intake was 'discontinuing medication during weekends and holidays'. This was also shown by scores on MARS items 3 and 4, were 28% sometimes to always stopped taking medication for a while, and 25% decided to miss out a dose. Stopping during weekends and holidays is suggested by the Dutch general practice guidelines for ADHD treatment in children, if school problems are the main issue, because pharmacological treatment of ADHD is mainly aimed to control symptoms.[6] As stimulants have a fast onset of action, the actual impact of non-adherence on overall efficacy might be relatively low. There is, however, also a debate about intermittent use as this can result in both withdrawal and first dose symptoms. Other reasons for a so-called 'drug holiday' are to test whether medication is still needed and to manage side effects, for example, reduce insomnia and appetite suppression, while ADHD symptoms are not increasing.[30,31] Weekends and holidays also have a different daily routine, which might negatively affect medication intake.[32] The exact reason for stopping during weekends or holidays and whether this was on the initiative of the adolescent or the physician's advice was not assessed in this study. Therefore, stopping during weekends or holidays will not always be a non-adherent behaviour.

A recent study of Emilsson *et al*. (2016) showed high adherence rates among adolescents with ADHD (88%); they focused on the mean MARS score in comparing to the total score.[28] If we focus on the mean MARS score of our study, an adherence rate of 85% is found. However, as the distribution of the total MARS score is very skewed, using a cut-off is more appropriate to calculate (non)adherence based on the MARS. If we apply the MARS cutoff (≥23) to the study of Emilsson *et al*. an adherence rate of 47% is found which is in line with our study, where 39% mentioned to be adherent (based on the MARS). Our findings are also in line with previous studies focusing on adolescents with other chronic diseases, such as asthma and diabetes, were adherence rates are often below 50%.[32,33]

Adherence is a complex phenomenon, and during adolescence, it might be even more complex since children become independent during this life phase. Other characteristics of adolescents are the tendency toward oppositional behaviour and the importance of peers in developing their social identity.[34,35] Taking medication does not fit in the self-image of most adolescents, potentially resulting in lower adherence rates compared with adults. Side effects are commonly reported for ADHD medication and might also affect adherence.[9,27,36] In our study, half of the participants (51.4%) reported decreased appetite and sleep problems. Surprisingly these frequent side effects do not really seem to affect adolescent's concerns about treatment, which are relatively low. Moreover, the majority of our study population reported a good to excellent overall health status.

The highest score on the items of the Brief-IPQ was on 'treatment control'. Thus, adolescents do think their medication is effective, despite the indifferent drug attitude. This surprising finding might indicate that adolescents do not see the importance of their ADHD medication. The positive thoughts about the efficacy of medication are in line with reports from other studies.[37,38] This creates an opportunity to improve ADHD treatment; those who treat adolescents with ADHD should support their patients' necessity beliefs and make them more aware of their positive medication attitude. A suggestion to achieve this is via shared decision-making, which might increase the adolescent's sense of autonomy. Future work should focus on the effectiveness of this shared decision-making on medication intake behaviour.

Our study included a large sample of adolescents (N=181) using ADHD medication. The mean age was 14.2 years, which deviates from other studies toward children using ADHD medication (9.7 years).[9] The participation rate of the pharmacies was low, because only 68 (out of 1,300) pharmacies participated. This might be due to the specific time window of the study or due to the invitation by a single e-mail which might end up in spam or remain unnoticed. However, the participating pharmacies are a representative sample of Dutch community pharmacies,[17] and 1,200 adolescents were invited from those pharmacies.

A response rate around 15% to 20% is often seen in studies focusing on adolescents. In our study, the patient response rate was 15%. If we focus on the self-reported substances of abuse (***Table 1***), our study population is largely comparable to the Dutch adolescent population (age 12-16 years); 25.5% of the Dutch adolescents drink alcohol and 10.6% smoke.[39] Furthermore, the mean age of our sample was 14.2 years and most of them used methylphenidate; this is in line with the highest use of methylphenidate at age 14 years.[16] Nonetheless, we have to be aware of participation bias due to self-selection. Thus, adolescents who are more aware of their medication and disease might probably be more eager to participate. This might result in a slightly overestimation of our results for the total adolescent ADHD population.

To ensure the diagnoses of ADHD, we selected adolescents based on filling of at least two prescriptions for methylphenidate, dexamphetamine, and/or atomoxetine in the preceding year. In the Netherlands, one prescription covers three months of medication use; therefore, the participants used ADHD medication at least for half a year. Unfortunately, the diagnosis ADHD is not verified by a physician. Another limitation is that our results are solely based on self-reported measurements, which may be subjected to social desirability bias. However, if we focus on, for example, the MARS score, the mean score (21.1 ± 3.0) does not suggest that adolescents using ADHD medication are always adherent, which is in line with previous adherence studies based on direct measurements.

In this study, most adolescents using ADHD medication had an indifferent drug attitude (perceived low concerns and low necessity). They mentioned frequently skipping medication doses, both

intentionally (e.g. weekends and holidays) and unintentionally (forgetfulness). Adolescents also frequently experienced side effects, although this did not result in high concerns towards the treatment. These findings should be taken into account when treating adolescents with ADHD. A suggestion to improve the treatment of ADHD might be to continuously combine pharmacological treatment with psychological and behavioural treatments.[40] Furthermore, monitoring and discussing the experiences of patients with their ADHD medication might be useful to optimize the treatment for adolescents with ADHD; pharmacists might play a role in this.

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CHAPTER 3.3

Asthma control and quality of life in adolescents: the role of illness perceptions, medication beliefs, and adherence

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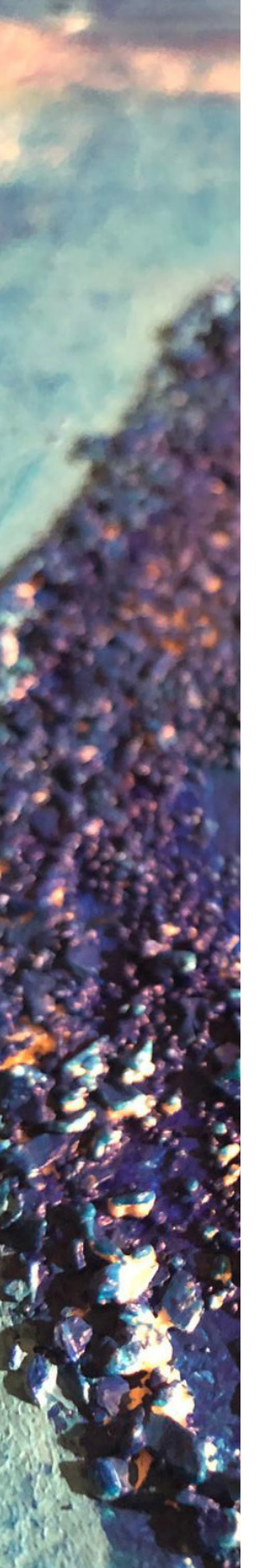


ABSTRACT

Objective: Asthma control and asthma related quality of life are important disease outcomes for patients with asthma. Illness perceptions and medication beliefs have been found to be important determinants of medication adherence, and subsequently asthma control and quality of life in adults with asthma. In adolescents, this issue needs further elucidation. Therefore the aim of the current study was to study the associations between illness perceptions, medication beliefs, medication adherence, disease control, and quality of life in adolescents with asthma.

Methods: In this cross-sectional study, we used baseline data of adolescents with asthma (age 12 - 18 years) who participated in the ADolescent Adherence Patient Tool (ADAPT) study. Questionnaires were administered online and included sociodemographic variables and validated questionnaires measuring illness perceptions, medication beliefs, self-reported adherence, disease control, and quality of life.

Results: Data of 243 adolescents were available (age 15.1 ± 2.0 years; 53% females). More than half of these adolescents (62%; n=151) reported to be non-adherent, 77% (n=188) had uncontrolled asthma, 43% (n=104) reported high necessity medication beliefs, and 95% (n=232) perceived low concerns about their asthma medication. There was a strong positive correlation between asthma control and quality of life (r=0.74). Illness perceptions and adherence were correlated with both asthma control and quality of life, with the strongest correlation between identity (symptom perception) and quality of life (r=-0.66). Medication beliefs were only associated with adherence (r=0.38).

Conclusion: In adolescents with asthma, there are complex associations between illness perceptions, medication beliefs, adherence, disease control, and quality of life.

INTRODUCTION

Disease control is an important outcome for patients with chronic conditions. Obtaining sufficient asthma control implies less asthma symptoms and exacerbations, decreased use of rescue medication, and improved quality of life.[1,2] A number of factors are related to uncontrolled asthma, among which are smoking, allergic rhinitis, female gender, and poor adherence.[3-6] Medication adherence is in particular a strong determinant of asthma control, because daily use of inhaled corticosteroids (ICS) suppresses the chronic airway inflammation.[7,8]

Adherence to medication is complex and affected by multiple factors.[9-11] Non-adherence is caused by a combination of unintentional (related to practical barriers) and intentional (related to motivation and beliefs) barriers to take medication.[4] The Common Sense Model of Self-Regulation (CSM) describes that illness perceptions and medication beliefs can affect intentional non-adherence.[12]

Adherence rates in asthma patients are generally low, e.g. on average 50% of asthma patients are adherent. It has been reported that adherence is especially low during adolescence.[13] Adolescents have specific barriers for medication adherence (e.g. they often forget to take their medication) and they have unique medication beliefs (e.g. girl aged 14 years: *"There are moments I do not feel better from using my inhaler, those times I use nothing"*).[14-16] Additionally a large proportion of adolescents experience a reduction of asthma symptoms.[17] This may affect their medication adherence, illness perceptions, and medication beliefs.

Factors, such as self-efficacy and perceptions on the illness and medication, have been shown to be important determinants for medication adherence and asthma control in adolescents.[18] However, the exact relation between illness perceptions, medication beliefs, and adherence (and subsequently asthma control and quality of life) is unknown. Clarification of this relation may improve the understanding of how disease control can be achieved, and thereby provide valuable insights for future interventions aimed at improving asthma control.[19] Therefore the aim of this study was to explore the associations between illness perceptions, medication beliefs, medication adherence, disease control, and quality of life in adolescents with asthma.

METHOD

Study design, population, and setting

In this cross-sectional study we used baseline data of patients who participated in the ADolescent Adherence Patient Tool (ADAPT) study. The complete rationale and design of the ADAPT study are described elsewhere.[20] In short: adolescents aged 12 - 18 years who filled two or more prescriptions for ICS during the previous 12 months were recruited from community pharmacies belonging to the Utrecht Pharmacy Practice network for Education and Research (UPPER).[21]

After signing informed consent, an online questionnaire was completed at the start of the study. For patients younger than 16 years, both parents also had to sign informed consent. Baseline data were collected between July 2015 and February 2016. The ADAPT study is approved by the Medical Review Ethics Committee of the University Medical Centre Utrecht (NL50997.041.14) and by the Institutional Review Board of UPPER, Department of Pharmaceutical Sciences, Utrecht University. The ADAPT trial is registered at the Dutch Trial Register (NTR5061).

Questionnaire items

The online questionnaire contained sociodemographic questions (e.g. age, gender, education, sport participation) and questions on adolescents' health status and asthma medication use. It also contained validated questionnaires on illness perceptions (Brief Illness Perception Questionnaire [Brief-IPQ]),[22] medication beliefs about ICS (Beliefs about Medicines Questionnaire-specific [BMQ-specific]),[23] adherence (Medication Adherence Report Scale [MARS]),[10] disease control (Control of Allergic Rhinitis and Asthma Test [CARAT]),[24] and asthma-related quality of life (Paediatric Asthma Quality of Life Questionnaire [PAQLQ]).[25]

Outcomes measures

The *Brief-IPQ* was used to assess adolescents' illness perceptions. This questionnaire consists of eight 11-point Likert scale items divided in three domains: cognitive representation, illness comprehensibility, and emotional representation. The ninth item was an open-ended item about the causes of the illness. We excluded this open-ended item from the analysis, because this item was perceived as complicated by young adolescents. For the other items, a total score between 0 and 10 was obtained, where a higher score represented more agreement with the item.

The *BMQ-specific* was used to assess adolescents beliefs about the necessity and concerns regarding their ICS asthma treatment. This questionnaire consists of ten questions, divided in two subscales; five items on necessity and five items on concerns. All items are scored on a five-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree), resulting in a total score between 5 and 25 per subscale. Scores above the scale midpoint (>15) were considered as strong beliefs, resulting in four attitudinal groups: accepting (high necessity, low concerns), ambivalent (high necessity, high concerns), indifferent (low necessity, low concerns), and sceptical (low necessity, high concerns).[26]

Self-reported ICS adherence was assessed using the *MARS*, which consists of five items. All items were scored on a five-point Likert scale ranging from 1 (always) to 5 (never), with a total score between 5 (not adherent) and 25 (completely adherent). Additionally, MARS scores were dichotomized by using a threshold of ≥23 for sufficient adherence, based on previous studies.[7,27]

Disease control was assessed using the *CARAT*, which consists of ten items. A total score between 0 and 30 was obtained, where scores >24 indicate good disease control. The total score can be divided

in allergic rhinitis symptoms (items 1 - 4, score >8 indicate good control) and asthma symptoms (items 5 - 10, ≥16 indicate good control).

Asthma related quality of life was assessed using the *PAQLQ,* which consists of 23 items divided in three domains: symptoms, activity limitations, and emotional function. All items were scored using a seven-point Likert scale, resulting in a total mean score (and per domain) between 1 and 7, where seven indicated the highest quality of life.

Data analysis

Descriptive statistics were calculated. For skewed data, the median with interquartile range (IQR) is shown instead of the mean with standard deviation (SD). Fitting (generalized) linear models were used for regression analyses and Pearson correlation coefficients were calculated. We used the Kruskal-Wallis test to test for differences between the four attitudinal groups. Statistical analysis were performed using R (version 3.4.3). P-values <0.05 were considered statistically significant.

RESULTS

In total 1,204 adolescents were invited to participate in the ADAPT study of which 243 adolescents (20.2%) from 54 pharmacies completed the baseline study measurement (on average 4.5 ± 2.7 adolescents per pharmacy). The characteristics of the study population are shown in ***Table 1***: half of the patients were male (46.9%), the mean age was 15.1 years, and most had a Dutch ethnicity (88.5%). A small number of patients (n=15) reported not having been diagnosed with asthma, however they did report potential symptoms of asthma such as shortness of breath (n=12), allergy symptoms (n=6), and/or exercise induced symptoms (n=3).

Almost half of the adolescents (44.0%) used asthma medication for more than 10 years. Four patients reported that they did not use their inhaler in the previous six months, because they ('thought they') did not need it (n=3) or forgot to take it (n=1). All remaining patients used ICS; either monotherapy or ICS in fixed combination with a long-acting beta-agonist (***Table 1***).

Table 1. Basic characteristics of the study population (N=243)

	% (n)
Male gender	**46.9 (114)**
Age, mean (SD)	**15.1 (2.0)**
Dutch ethnicity[a]	**88.5 (215)**
Environment	
Rural	51.4 (125)
Urban	45.3 (110)
Other	3.3 (8)
Education	
Elementary school	4.1 (10)
High school: vocational level	25.1 (61)
High school: pre-university level	53.9 (131)
Other	16.9 (41)
Lifestyle	
Alcohol use	34.2 (83)
Tobacco use	4.5 (11)
Playing sports	81.9 (199)
Sport hours per week, mean (SD)	4.7 (2.8)
Self-reported health status	
Very good to excellent	32.9 (80)
Good	53.1 (129)
Bad to moderate	14.0 (34)
Asthma diagnosis	**93.8 (228)**
Asthma age (n=223)[b], mean (SD)	7.5 (4.8)
Asthma family history (n=145)	**59.7 (145)**
Father	34.5 (50)
Mother	42.1 (61)
Sibling	34.5 (50)
Medication used (n=239)[c]	**98.4 (239)**
ICS	100 (239)
SABA	74.5 (178)
LABA	46.9 (112)
Adherent (MARS)	**37.9 (92)**
Well-controlled disease (CARAT)	**22.6 (55)**
Well-controlled asthma	21.8 (53)
Well-controlled allergic rhinitis	38.3 (93)

[a] Adolescent and both parents have Dutch ethnicity.
[b] n=5 age unknown.
[c] Self-reported data on the previous six months.

CARAT, Control of Allergic Rhinitis and Asthma Test; ICS, inhaled corticosteroids; LABA, long-acting beta-agonist; MARS, Medication Adherence Report Scale; SABA, short-acting beta-agonist; SD, standard deviation.

Illness perceptions

Adolescents scored the highest on timeline (i.e. *how long do you think your illness will continue?*), indicating that they expected a chronic course of their illness. Thereafter the highest scores were obtained for personal control, treatment control, and coherence (i.e. *how well do you feel you understand your illness?*). The lowest scores were on the domain emotional representation, suggesting that their asthma did not emotionally affect them (***Table 2***).

Table 2. The median score and correlation coefficients per item of the Brief Illness Perception Questionnaire (Brief-IPQ); response scale 0 (not at all) to 10 (very much).

Domain	Item	Question	Median (IQR)	*Necessity-concerns*	*Adherence*	*Disease control*	*Quality of life*
Cognitive illness representations	Consequences	How much does your illness affect your life?	3 (5)	-0.01	-0.08	-0.48*	-0.53*
	Timeline	How long do you think your illness will continue?	9 (4)	0.25*	0.01	-0.25*	-0.22*
	Personal control	How much control do you feel you have over your illness?	8 (3)	-0.01	0.09	0.45*	0.45*
	Treatment control	How much do you think your medication can help your illness?	8 (3)	0.28*	0.30*	0.41*	0.41*
	Identity	How much do you experience symptoms from your illness?	3 (4)	0.05	-0.11	-0.54*	-0.66*
Illness comprehensibility	Coherence	How well do you feel you understand your illness?	8 (4)	0.09	0.13*	0.23*	0.22*
Emotional representations	Emotional representation	How much does your illness affect you emotionally? (e.g. does it make you angry, scared, upset or depressed?)	1 (3)	-0.09	-0.11	-0.44*	-0.63*
	Illness concern	How concerned are you about your illness?	1 (3)	-0.03	-0.07	-0.50*	-0.64*

* Significant correlations ($p<0.05$).

IQR, Interquartile range.

Beliefs about medication

The mean BMQ-necessity score was 14.4 ± 5.1 (range 5 - 25) and the mean BMQ-concerns score was 9.2 ± 3.4 (range 5 - 23). Almost half of the adolescents (42.8%; n=104) reported high necessity beliefs (above scale midpoint), while only 11 adolescents (4.5%) reporting high concerns. Subsequently the majority of adolescents had a positive necessity-concern differential (81.9%; n=199) and most adolescents had an indifferent or accepting attitude (***Figure 1***). There were significant differences between the percentages of controlled (p=0.047) and adherent (p=0.002) patients in the four attitudinal groups (***Figure 1***).

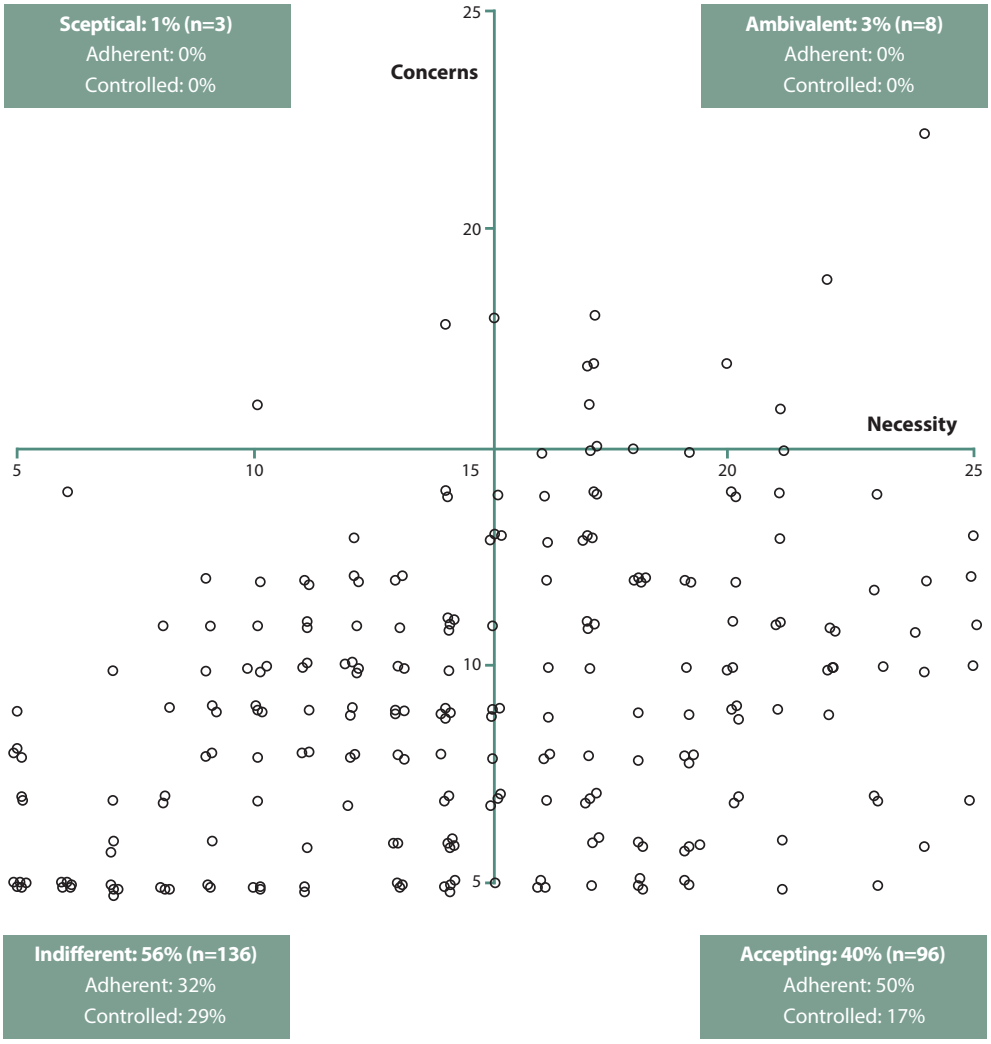


Figure 1. Scatter plot of the Beliefs about Medicines Questionnaire (BMQ) necessity and concern scores, divided in four attitudinal groups with their corresponding percentage of adherent (Medication Adherence Report Scale [MARS] ≥ 23) and disease controlled patients (Control of Allergic Rhinitis and Asthma Test [CARAT] > 24).

Self-reported medication adherence

The median MARS score was 22.0 (IQR 5) and 37.9% (n=92) of the adolescents were defined as adherent, i.e. scored above the threshold (MARS ≥23). The percentage of adolescents scoring 1 to 3 (always to sometimes) was the highest at item 1, 3, and 5 (***Table 3***). The median of intentional non-adherence (items 2 - 5) was five, whereas the median of unintentional non-adherence, i.e. forgetting, was three.

Table 3. The median Medication Adherence Report Scale (MARS) scores per item, ranging from 1 (always) to 5 (never), and the percentage of patients (N=243) scoring 1 (always) to 3 (sometimes).

MARS items	Median (IQR)	Scoring 1-3 % (n)
1. I forget to take my medicines	3 (1)	53.9 (131)
2. I change the dosage of my medicines	5 (1)	21.4 (52)
3. I stop taking my medicines for a while	5 (2)	27.6 (67)
4. I decide to skip one of my medication dosages	5 (1)	16.9 (41)
5. I use my medication less than is prescribed	5 (1)	23.5 (57)

IQR, Interquartile range; MARS, Medication Adherence Report Scale.

Self-reported disease control

In total, 22.6% of the adolescents (n=55) had sufficient disease control (CARAT >24), with more adolescents having control over allergic rhinitis symptoms (38.3%), than over asthma symptoms (21.8%; ***Table 1***). The mean CARAT score was 19.6 ± 5.5 (range 0 - 30), the mean allergic rhinitis score was 7.2 ± 3.1 (range 0 - 12), and the mean asthma score was 12.4 ± 3.6 (range 0 - 18). All these means were below the standardized thresholds for sufficient control.

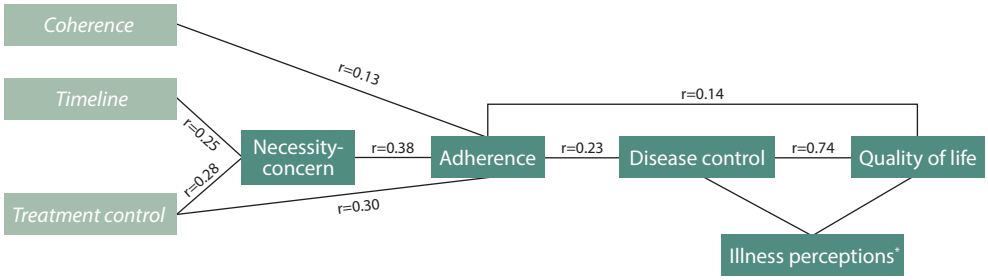
Asthma related quality of life

The mean total PAQLQ score was 5.9 ± 0.9 (range 1.4 - 7.0). The highest mean score was on emotional function 6.5 ± 0.9 (range 1.4 - 7.0), thereafter on symptoms 5.7 ± 1.1 (range 1.4 - 7.0), and subsequently on activity limitation 5.4 ± 1.1 (range 1.4 - 7.0).

Associations illness perceptions, medication beliefs, adherence, asthma control, and quality of life

All associations are summarized in ***Figure 2*** (and ***Appendix 1***). There was a strong correlation (r=0.74) between disease control and quality of life (p<0.001). A weak correlation was found between adherence and the necessity-concern differential (r=0.38; p<0.001), thus necessity was positively correlated with adherence (r=0.28; p<0.001), while concerns were negatively correlated (r=-0.14; p=0.026). Other weak correlations were found between adherence and disease control (r=0.23; p<0.001), and adherence and quality of life (r=0.14; p=0.035). Within the PAQLQ domains, only 'symptoms' was correlated with adherence (r=0.14; p=0.027).

All illness perception items were correlated with disease control and quality of life (***Table 2***), with the strongest correlations between identity (i.e. symptom perception) and quality of life (r=-0.66; p<0.001), illness concern and quality of life (r=-0.64; p<0.001), and emotional representation and quality of life (r=-0.63; p<0.001). Indicating that more asthma symptoms, more concerns, and more emotionally affect are associated with a decrease in quality of life. Duration of the illness (timeline; r=0.25; p<0.001) and treatment control (r=0.28; p<0.001) were both also correlated with the necessity-concern differential. Moreover, treatment control (r=0.30; p<0.001) and coherence (i.e. *how well do you feel you understand your illness?;* r=0.13; p=0.045) were weakly correlated with adherence (***Figure 2***).



r, correlation coefficient.

* All items of the Brief Illness Perception Questionnaire were correlated with disease control and quality of life (***Table 2***).

Figure 2. Associations between medication beliefs, adherence, illness perceptions, disease control, and quality of life in adolescents with asthma (N=243).

Adherent adolescents (MARS ≥23; n=92) had significant higher scores on the CARAT (median 21) compared to the non-adherent adolescents (n=151; median 19; p=0.006). The asthma control subscale was significantly higher (median 14 versus 13; p=0.007), while there was no difference on the allergic rhinitis subscale (p=0.082). Remarkably, 21% of non-adherent patients had controlled asthma and 75% of adherent patients had uncontrolled asthma. These findings support the weak correlation between adherence and disease control (r=0.23; ***Figure 2***). Moreover, adherent adolescents had a higher necessity-concern differential (median 7.0 versus 3.0; p<0.001) and a higher quality of life score (median 6.4 versus 6.0; p=0.004). They perceived more personal control (median 8 versus 7; p=0.009) and more treatment control (median 8 versus 7; p<0.001) than non-adherent adolescents. Adherent adolescents also perceived less symptoms (identity; median 2 versus 3, p=0.003) and were less emotionally affected by their asthma (median 0 versus 1, p=0.006) compared to non-adherent adolescents.

Adolescents with disease control (CARAT >24; n=55) had a higher quality of life (median 6.7) compared to those without disease control (n=188; median 5.9; p<0.001). No differences were found in the medication beliefs (necessity-concern differential; p=0.359) and adherence scores (p=0.089). However, patients with disease control had higher scores on personal control, treatment control, and coherence, while they scored lower on consequences, timeline, identity, emotional representations, and illness concerns (coherence p=0.002; others p<0.001).

DISCUSSION

This study showed complex relations between illness perceptions, medication beliefs, medication adherence, asthma control, and quality of life in adolescents with asthma. Disease control and quality of life were highly correlated. Both adherence and illness perceptions were related to

these disease outcomes, while medication beliefs were only associated with adherence (***Figure 2***). Necessity beliefs were positively associated with adherence, while concerns were negatively associated, which is also previously shown.[10,28] Remarkably, adherence was only correlated to the disease outcomes, i.e. asthma control and quality of life.

Most illness perceptions were not associated with adherence in the current study. This finding is contradictory to the CSM,[12] which proposes that cognitive and emotional representations towards a health threat result in illness perceptions and medication beliefs, which affect health behaviour (e.g. adherence). Only 'treatment control' (i.e. *how much do you think your medication can help your illness?*) and 'coherence perceptions' (i.e. *how well do you feel you understand your illness?*) were slightly associated with adherence, which is shown before.[29] Medication beliefs of adolescents with asthma were associated with adherence, which is in line with the CSM and previous studies.[11]

Adherence and illness perceptions were associated with disease outcomes, such as asthma control and quality of life.[30] These findings suggest that improving patient's behaviour (increasing adherence) and their illness perceptions (improving cognitive illness representations and illness comprehensibility; ***Figure 2***) might improve disease outcomes of adolescents with asthma. However, compared to adults and adolescents with other chronic conditions, adolescents with asthma had already high personal control and coherence, and low concerns and consequences.[31] Thus, there was not much to achieve in the illness perception of the current study population. However, adherence could be increased, as only 38% was defined as adherent. A suggestion to improve adolescent's behaviour and their illness perceptions is to use online influencer (i.e. someone who affects the way other people behave, via use of social media), as for example celebrities with chronic conditions can motivate patients in using their medication and improve their illness perceptions.[32]

More than half of the current adolescent population (56%) had an indifferent attitude (low necessity and low concerns; ***Figure 1***), which makes it hard to motivate them. This indifferent attitude might be age-specific, or it might be caused by their long-term medication use; 44% used asthma medication for more than 10 years. The indifference could also be related to the high control perceptions (personal and treatment control) and low symptom perceptions (identity), i.e. they were feeling fine. However, only 23% of the adolescents had indeed sufficient disease control. This discrepancy between perceived and reported asthma control, suggests that it is important to improve adolescent's insights into their asthma control. For example by comparing their perceived asthma control with objectively measured asthma control. These improved insights might increase treatment necessity beliefs and treatment control perceptions (and thereby may subsequently support adherence and asthma control). However, more research is needed to find effective ways to improve adolescent's insights into their asthma control.

The current study emphasized the complex relation between medication adherence and disease control. Most adolescents in this study were non-adherent and had uncontrolled asthma, however

21% of the non-adherent adolescents had controlled asthma. This contradictory finding might be caused by the mechanism of action of ICS. Patients are advised to use daily controller medication to suppress their chronic airway inflammation. However, when they sometimes forget to use ICS, they will not directly experience wheezing or other asthma symptoms. Moreover, the transition of asthma symptoms (i.e. decrease during adolescence)[17] might also explain why some non-adherent patients still had disease control. These patients may be overtreated. On the other hand, 75% of adherent patients had uncontrolled asthma. These patients require special attention, because other factors may contribute to uncontrolled asthma, such as wrong inhaler techniques, seasonal effects, too low dose of ICS, or uncontrolled allergic rhinitis.

Weak correlations were found in this study, suggesting complex relations. We suggest that 'feedback mechanisms' might play a role here. For example, patients are adherent till a certain level of disease control, thereafter they become more negligent with their asthma medication (as they experience less asthma symptoms). To illustrate; the percentage of adherent patients in the indifferent group (32%) was lower than in the accepting group (50%), while the percentage of controlled patients (29%) was higher in the indifferent group than in the accepting group (17%); ***Figure 1***. Such mechanisms may make it hard to obtain complete disease control, because patients can become more indifferent towards their medication when they experience less asthma symptoms.

This cross sectional study used validated questionnaires to measure study outcomes, which has some limitations. First of all, there might be a desirability bias. Preferably we had applied additional direct measurements, such as refill records for adherence and forced expiratory volume (FEV_1) measurements for asthma control. Secondly, the participants in the current study participated in a clinical trial, suggesting that they were highly motivated (participation bias). This might partly explain why almost half of the adolescents (43%) reported high necessity beliefs and 82% had a positive necessity-concern differential. The latter percentage is high compared to other adolescent patient populations, as for example 62% of adolescents with ADHD had a positive necessity-concern differential and 11% reported high necessity beliefs (***Chapter 3.2***).[33] Moreover, our findings are population based, while there are always variations between patients, suggesting that there is ample room to discuss the specific illness perceptions and medication beliefs of individual adolescents.

Adolescents with asthma reported low adherence rates and poor disease control, while they had a high quality of life, high necessity beliefs, and low emotional asthma representation. Complex relations were found between illness perceptions, medication beliefs, medication adherence, and subsequently asthma control and quality of life in adolescents with asthma. Influencing illness perceptions and improving medication adherence (via medication beliefs) may subsequently improve disease control and quality of life in adolescents with asthma.

ACKNOWLEDGEMENTS

The authors would like to thank the participants for their input.

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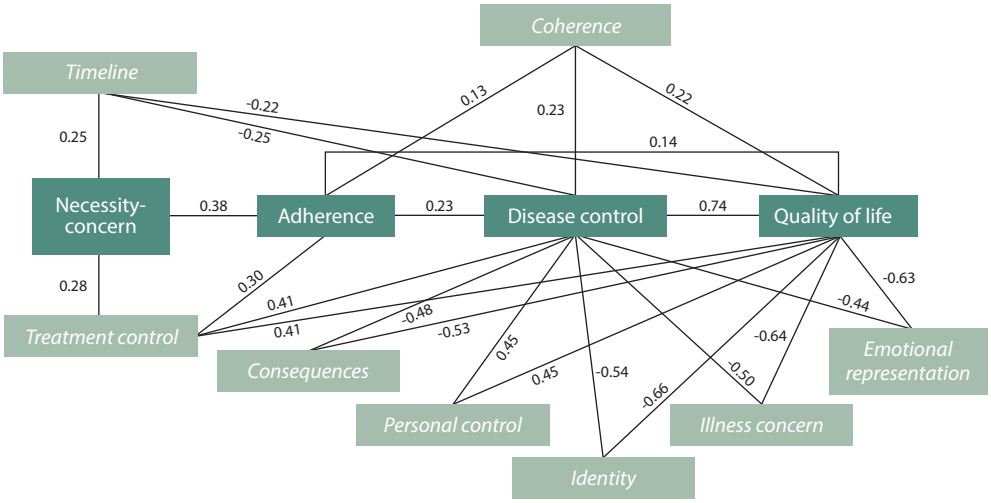
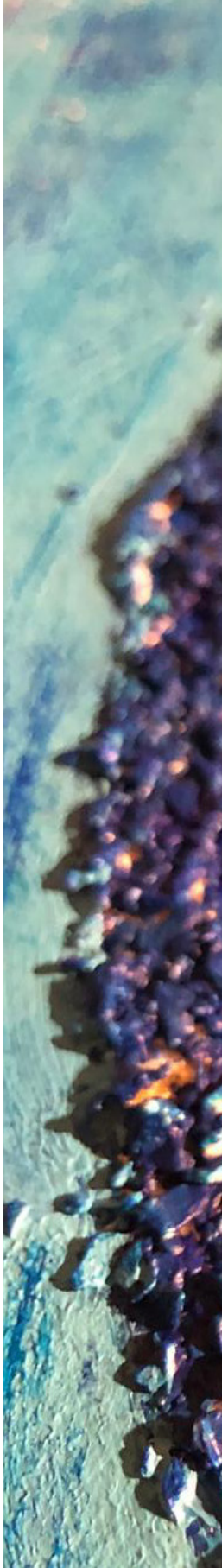
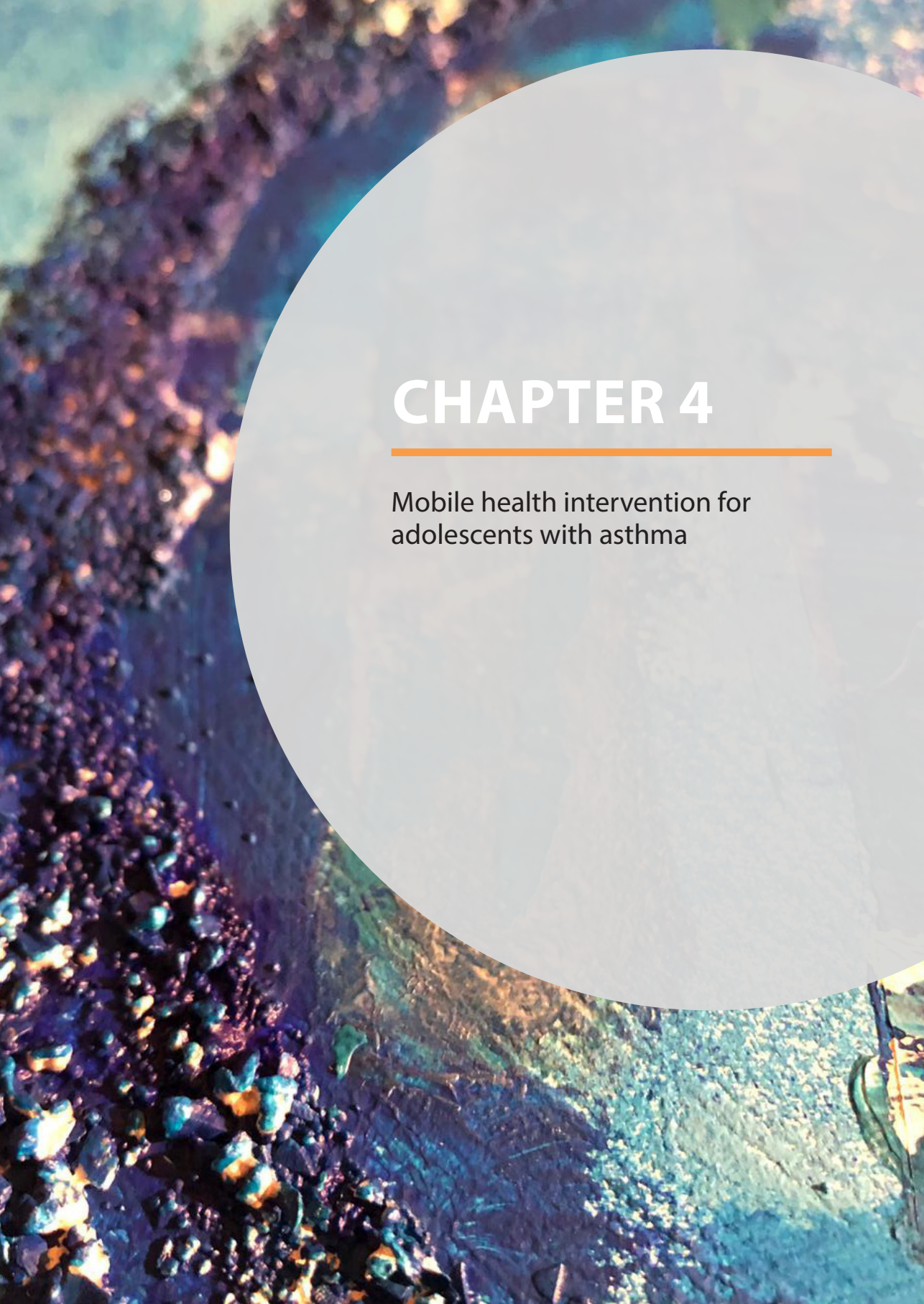
APPENDIX



Appendix 1. Correlations between medication beliefs, adherence, disease control, quality of life, and all illness perceptions (*Italic*) in adolescents with asthma.





CHAPTER 4

Mobile health intervention for adolescents with asthma

CHAPTER 4.1

MHealth intervention to support asthma self-management in adolescents: the ADAPT study

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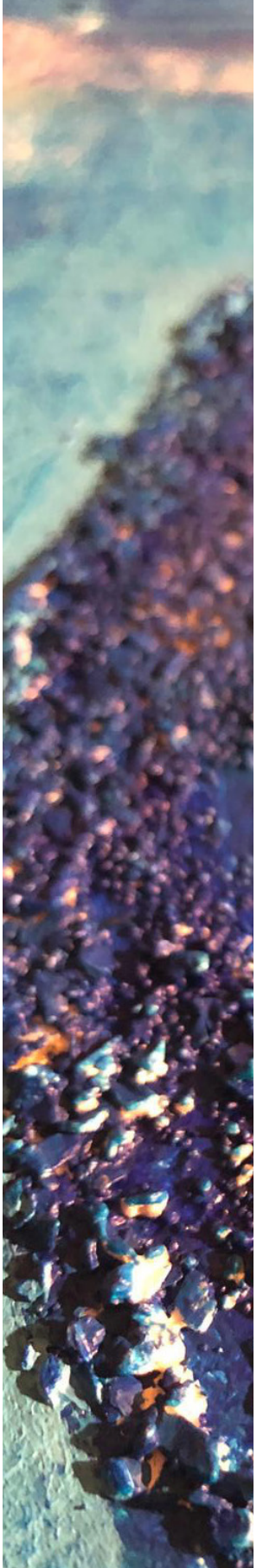

ABSTRACT

Purpose: Poor medication adherence in adolescents with asthma results in poorly controlled disease and increased morbidity. The aim of the ADolescent Adherence Patient Tool (ADAPT) study is to develop a mobile health (mHealth) intervention to support self-management and to evaluate the effectiveness in improving medication adherence and asthma control.

Intervention: The ADAPT intervention consists of an interactive smartphone application (app) connected to a desktop application for healthcare providers, in this study, the community pharmacist. The app contains several functions to improve adherence as follows: 1) a questionnaire function to rate asthma symptoms and monitor these over time; 2) short movie clips with medication and disease information; 3) a medication reminder; 4) a chat function with peers; and 5) a chat function with the pharmacist. The pharmacist receives data from the patient's app through the desktop application, which enables the pharmacist to send information and feedback to the patient.

Study design: The ADAPT intervention is tested in a community pharmacy-based cluster randomised controlled trial in the Netherlands, aiming to include 352 adolescents with asthma. The main outcome is adherence, measured by patient's self-report and refill adherence calculated from pharmacy dispensing records. In addition, asthma control, illness perceptions, medication beliefs, and asthma-related quality of life are measured.

Conclusion: This study will provide in-depth knowledge on the effectiveness of a mHealth intervention to support asthma self-management in adolescents. These insights will also be useful for adolescents with other chronic diseases.

INTRODUCTION

The estimated adherence rates with inhaled corticosteroids (ICS) vary between 30% and 70%.[1] These low adherence rates result in uncontrolled asthma and unnecessary hospitalizations, associated with decreased quality of life and school and work absenteeism.[2-4] Poor adherence is a complex problem that can be divided into intentional (consciously deciding) and unintentional (forgetting or not being able to use medicines) non-adherence behaviour.[5]

Adherence rates decline during adolescence; studies report adherence rates of 50% at age 12, while rates <20% are found at age 17.[6,7] During this life phase, adolescents become more responsible for their own medication use, which can affect their medication intake behaviour.[7] As adolescents perceive low necessity toward their medication use,[8] positively affecting adolescents' beliefs toward illness and treatment might result in increased adherence rates.[9-12]

The Common Sense Model of Self-Regulation (CSM) describes that illness perceptions and medication beliefs can affect adherence.[13] This model has been extensively used to describe health behaviour related to health threats.[14] It proposes cognitive and emotional representations toward the health threat, resulting in illness perceptions and medication beliefs, which affect health behaviour (e.g. adherence). This is a continuous process, allowing modifications of the representations and coping mechanisms.[15] Therefore, affecting cognitive or emotional representations might result in a health behaviour change.

Numerous interventions have been developed to increase medication adherence; however, study results are inconsistent and show low effectiveness for most interventions.[16] Interventions tailored to individual's needs are suggested to be more effective, because every individual might need a different approach to tackle his or her specific intentional and unintentional barriers affecting adherence.[17] Most existing interventions to improve asthma medication adherence are intended for adults or children, and interventions among adolescents with asthma are scarce.[16]

To assess the specific needs and preferences of adolescents with asthma, we conducted a focus group study. In line with previous studies, this study revealed forgetting as a major reason for ICS non-adherence.[18-20] The adolescents who participated in the focus group study recommended a smartphone application (app) as an intervention to support self-management. Peer support and personalised medication reminders were suggested as important parts of this intervention.[21]

In the Netherlands, 96% of the adolescents have a smartphone,[22] suggesting that an app might be an appropriate intervention for adolescents. Although different mobile self-management applications for asthma exist, most of these interventions are not specifically intended for adolescents.[23,24] Therefore, the ADolescent Adherence Patient Tool (ADAPT) is developed. The aim of our study is to evaluate the effectiveness of the ADAPT intervention to improve adherence and asthma control in adolescents with asthma.

METHODS AND DESIGN

Study design

Effectiveness of the ADAPT intervention is studied in a community pharmacy-based cluster randomised controlled trial. Community pharmacies affiliated with the Utrecht Pharmacy Practice network for Education and Research (UPPER) are approached to participate in the study.[25] The participating community pharmacies are randomly divided into a control (six months usual care) and an intervention group (six months use of the ADAPT intervention; ***Figure 1***). In the Netherlands, asthma usual care in pharmacies is defined as *"regularly repeating the inhalation instruction and signaling of excessive bronchodilator or insufficient ICS use"*.[26]

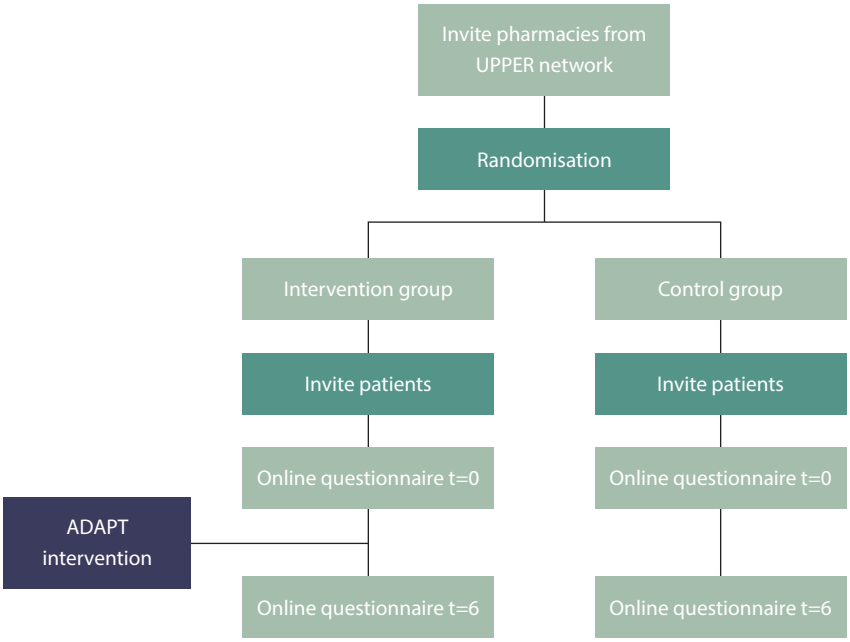

Figure 1. Design of the ADAPT asthma study.
ADAPT, ADolescent Adherence Patient Tool; UPPER, Utrecht Pharmacy Practice network for Education and Research.

Patients meeting the inclusion criteria, described in the following, receive a postal invitation and informed consent from their community pharmacy. For patients younger than 16 years, both parents and the patient have to sign informed consent. Upon receiving the signed informed consent, the first online questionnaire (baseline measurement) is sent via e-mail. At the end of follow-up (after six months), the second online questionnaire is sent. Completion of the online questionnaires is monitored, and e-mail reminders are sent when needed.

Participants

The participating pharmacies are spread across the Netherlands (***Figure 2***). Adolescents with asthma (age 12 - 18 years) are selected from the pharmacy information system based on medication dispensing records. Adolescents who fill two or more prescriptions for ICS or ICS in combination with a long-acting beta-agonist (ICS/LABA) during the previous 12 months are eligible for inclusion. The asthma diagnosis is verified by the patient's general practitioner. The possession of a smartphone is an additional inclusion criterion for the ADAPT study. Patients who use ICS for indications other than asthma, have insufficient comprehension of the Dutch language, or are unable to take medication themselves are excluded.

Figure 2. The ADAPT study locations in the Netherlands.
ADAPT, ADolescent Adherence Patient Tool.

Sample size

Medication Adherence Report Scale (MARS) scores are used to measure self-reported adherence at baseline and at the end of follow-up.[27] To detect a relevant difference (>1.5 ± 4.0) in MARS scores with a power of 80%, a significance level of 95%, and accounting for 35% dropout, 151 patients per group (intervention and control) are required. As a cluster randomised design is used, a correction factor of 1.16 is needed, based on inclusion of 10 patients and variation of 0.25 per pharmacy. This

results in a sample size of 175.2 patients per group; thus, a total of 352 patients have to be included. Based on previous experiences, we estimate that ~25 - 30 patients per pharmacy will meet the inclusion criteria; therefore, inclusion of 10 patients per pharmacy should be feasible.

Study outcomes

The primary study outcome is 'medication adherence' based on patient's self-report (measured with the MARS at baseline and at the end of follow-up) and five-year medication refill records. The secondary study outcome is asthma control. Moreover, asthma-related quality of life, medication beliefs, and illness perceptions are measured.

For all participants, data collection takes place through an online questionnaire at baseline (t=0) and at the end of follow-up (t=6). This online questionnaire contains questions regarding health-related quality of life (question derived from the RAND-36; developed by the RAND Corporation),[28] asthma and allergic rhinitis symptoms (Control of Allergic Rhinitis and Asthma Test [CARAT]),[29] asthma-related quality of life (Paediatric Asthma Quality of Life Questionnaire),[30] illness perceptions (Brief Illness Perception Questionnaire),[31] beliefs about medicines (Beliefs about Medicines Questionnaire-Specific),[32] and medication adherence (MARS).[27] The online questionnaire also contains sociodemographic questions. Additionally, five-year medication history of pharmacy dispensing records is extracted from the pharmacy information system to calculate ICS refill adherence and to evaluate the use of concomitant medication. A cost-effectiveness evaluation will be conducted at the end of the study.

Process evaluation

During the study, the actual use of the intervention by pharmacists and patients (filling out questionnaires and viewing movies) is monitored. When patients wish to withdraw from the study, the reason for discontinuation will be registered. Pharmacists are regularly contacted to get feedback on the implementation of the intervention. At the end of follow-up, both patients' and pharmacists' experiences, barriers/facilitators for further implementation, satisfaction with the intervention, and perceived effectiveness will be evaluated with a short online questionnaire (***Chapter 5***).

ADAPT intervention

The ADAPT intervention consists of a smartphone app for patients, which is securely connected to a desktop application for healthcare providers, in this study the community pharmacist (***Figure 3***). Patients can download the ADAPT smartphone app, which is freely available in the App Store and Play Store. A password – provided by the patient's healthcare provider – is necessary to gain access to the full functionality of the app and to connect the app to the desktop application used by the patient's community pharmacist. This password entry ensures that solely participants of the intervention group can make full use of the app. To ensure the patient's privacy, data are securely sent to the database and a personally chosen password is needed to access the app. The app contains different functionalities to stimulate self-management and improve adherence behaviour:

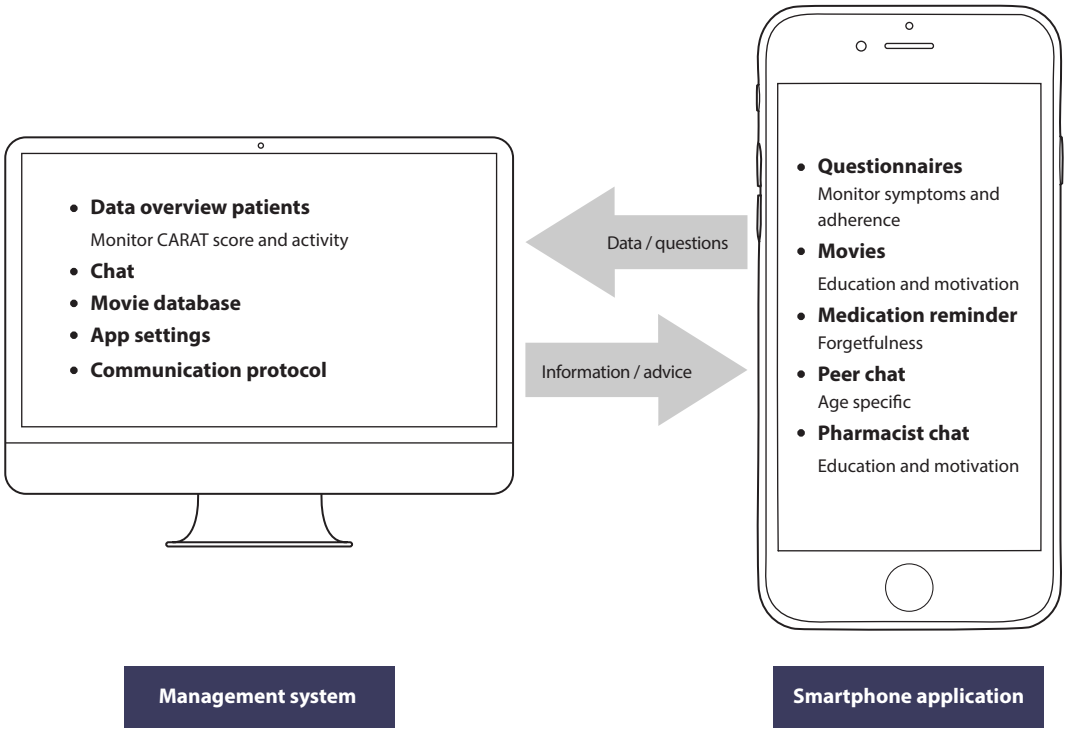

Figure 3. The interactive ADolescent Adherence Patient Tool (ADAPT) with the different functionalities.
App, smartphone application; CARAT, Control of Allergic Rhinitis and Asthma Test.

- This app helps in monitoring symptoms, with the CARAT. This questionnaire covers both allergic rhinitis and asthma symptoms (***Table 1***). A total score between 0 and 30 can be obtained, where scores >24 indicate good disease control. The total score can be divided into two subscores: an allergic rhinitis subscore (items 1 - 4, score >8 indicates good control) and an asthma subscore (items 5 - 10, score ≥16 indicates good control).[29] Patients are asked to complete the CARAT questionnaire at least every week, and they can generate a graphical display of their disease control over time. This may influence their emotional representation of their asthma and allergic rhinitis symptoms, which can modify illness perceptions and indirectly affect adherence.[13] The pharmacist can also monitor the CARAT scores through the linked desktop application.
- Short movies about different asthma-related topics, such as medication use and asthma triggers, are available next to more lifestyle-oriented movies on how to cope with asthma in daily life, such as smoking, going to school, and performing sports. These movies have been made with active participation of asthmatic adolescents. Patients occasionally receive new movies during the study or upon request, since pharmacists have access to a movie database. Pharmacists can choose to send, for example, an inhalation instruction

movie referring to the device that the patient is using. The short movies are an age- specific way to counsel patients and can affect the cognitive representation of asthma and medication use, which might result in increased adherence rates.

Table 1. Items of the Control of Allergic Rhinitis and Asthma Test (CARAT)

During the last week, because of your asthma/rhinitis/allergy, how many times, on average, did you experience:				
1. Blocked nose?	Never	Up to 2 days per week	More than 2 days per week	Almost every day or every day
2. Sneezing?				
3. Itchy nose?				
4. Runny nose?				
5. Shortness of breath/dyspnea?				
6. Wheezing in the chest?				
7. Chest tightness upon physical exercise?				
8. Tiredness/limitations in doing daily tasks?				
9. Waking up during the night because of your asthma/rhinitis/allergy?				
During the last week, because of your asthma/rhinitis/allergy, how many times did you have to:				
10. Increase the use of your medication?	I'm not taking any medicines	Never	Less than 3 days	3 or more days

- Medication reminder alarm, which is adjustable to the patient's preferences (timing and number of alerts) to prevent forgetting, i.e. unintentional non-adherence, is provided.
- This app contains a peer chat function to contact peers participating in the ADAPT study. The peer chat function gives the opportunity to share experiences and support each other; this might relieve the feelings of being different and unfairness,[33] which affect their emotional representation of asthma.
- This app has a pharmacist chat function to ask questions and facilitate easy access of information and guidance for the patient. Pharmacists are in the right position to recognise medication-related problems and counsel patients on their medication use; in the Netherlands, every patient is registered at a pharmacy and counseling is obligated when medication is dispensed for the first time. Usually, there is limited contact between pharmacists and adolescents since the parents often collect prescriptions at the pharmacy.[34] The pharmacist chat might bridge this gap, because it facilitates direct contact between the pharmacist and the adolescent. The patient's general practitioner will be contacted when pharmacists notice disease-related problems, thereby adolescent's access to healthcare providers will be improved.
- Two questions focusing on adherence (forgetting and intentionally skipping a dose) will appear randomly once every two weeks to gain insight into the adherence behaviour. Hereby, pharmacists have an indication of the type of non-adherent behaviour.

Pharmacists receive a desktop application: ADAPT Asthma PRO. After permission of the patient, the pharmacist is able to receive data and send information to the patient's app. The desktop application consists of the following elements:

- Overview of patient data, such as the patient's app use (activity and movies seen) and the CARAT symptom scores, graphically or in a table format. Pharmacists receive e-mail alerts when a patient's CARAT score is below the threshold. They can adjust the threshold, contact the patient, or inform the general practitioner when needed.
- Chat function to contact the patient about their CARAT score, their medication use, or their app use.
- Movie database, containing short movies covering different topics. The pharmacist has the opportunity to send specific movies to a patient, based on individual needs.
- Possibility to adjust settings of the individual patient app, such as the CARAT threshold, CARAT reminder interval, and the available movies for the patient.
- Communication protocol that supports pharmacists to interact effectively with adolescents.

All participating pharmacists receive a half-day training about asthma and medication use by adolescents, including tips for communication with this patient group. They also receive (on the spot) training and a manual on how to use the desktop application.

Ethics approval

The study is approved by the Medical Review Ethics Committee of the University Medical Centre Utrecht (NL50997.041.14) and by the Institutional Review Board of UPPER, Department of Pharmaceutical Sciences, Utrecht University. The trial is registered at the Dutch Trial Register (NTR5061). All participants have to complete informed consent before the start of the study.

DISCUSSION

We developed the ADAPT intervention – based on results of our previous focus group study and findings from literature – to improve adherence rates and asthma control in adolescents with asthma. Effectiveness of this intervention is studied in a community pharmacy-based cluster randomised controlled trial.

Unlike most existing interventions,[35-37] the interactive and adjustable ADAPT intervention consists of more than one element, targeting several aspects of non-adherence, thereby optimally supporting asthma self-management of individual patients. Previous studies showed that educational interventions alone are insufficient and that incorporating a behavioural component might increase the efficacy of adherence enhancing interventions.[17] Therefore, the ADAPT intervention combines

different components to positively affect medication intake behaviour, e.g. educational movies, a medication reminder, insight in recorded symptoms, easy access to healthcare providers, and a peer chat function. Based on the CSM, important characteristics for a patient-centered intervention are structured, flexible, and stimulate self-regulative control,[15] which are all applicable to the ADAPT intervention.

Development of the ADAPT intervention was based on needs and preferences of the target group, and was tested by a small group of adolescents before start of the study.[21] Moreover, the intervention is easy to implement in adolescent's daily life as most adolescents have a smartphone and continuously carry it with them. The app enables adolescents to independently manage their medication use, without the involvement of their parents.

Effectiveness of the intervention will be studied in daily practice in order to identify patient groups who benefit most. Therefore, the intervention is designed for all adolescents with asthma, regardless of their adherence level, disease severity, or disease control. This heterogeneity might limit the effectiveness of the intervention, since there is less to achieve in well-controlled asthma or adherent patients.

We aim to stimulate a uniform implementation of the intervention through training of pharmacists and a structured communication protocol to be used in the desktop application (***Figure 3***). However, pharmacists may differ in their ability and motivation to properly use the ADAPT intervention for support and counseling of adolescents. On the other hand, these differences in counseling also represent differences in daily patient care between pharmacies and thereby increase external validity. To account for this, we will evaluate the actual delivery of the intervention.

Another limitation is the voluntary usage of the app; when patients (in the intervention group) have access to the app, we asked them to complete the CARAT questionnaire at least every week. However, it is up to the patient to use the app. To prevent non-use, pharmacists receive the instruction to contact patients (e.g. via the chat function), when they rarely use the app. At the end of the study, we will ask patients about reasons for (not) using the app (***Chapter 5.1***).

Although study outcomes are mostly based on patient's self-report, validated questionnaires are used. Self-reported adherence is likely to result in an overestimation, and therefore, adherence is also calculated from five-year medication refill records.

CONCLUSION

Asthma affects millions of patients worldwide, and several studies have shown insufficient adherence rates resulting in poorly controlled asthma and decreased quality of life.[2-4] It is therefore

important to increase adherence. The ADAPT study will show whether a tailored smartphone app for adolescents with asthma is effective in improving adherence and disease control. In addition, the study will give detailed information on the implementation of a mobile health (mHealth) intervention in adolescents. These insights will also be useful for the development of mHealth interventions for adolescents with other chronic diseases.

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CHAPTER 4.2

Effect of a mHealth intervention on adherence in adolescents with asthma: a randomised controlled trial

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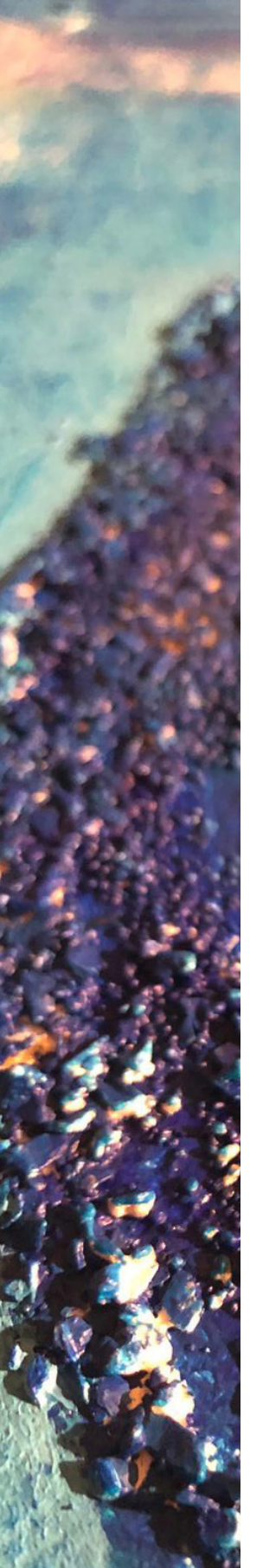
Under review by Respiratory Medicine



ABSTRACT

Background: Adherence rates among asthma patients are generally low and decrease during adolescence, resulting in poorly controlled asthma. The aim of our study was to evaluate the effectiveness of the ADolescent Adherence Patient Tool (ADAPT), an interactive mobile health (mHealth) intervention, in supporting self-management and improving inhaled corticosteroid adherence in adolescents with asthma.

Methods: We conducted a cluster randomised controlled trial in 66 Dutch community pharmacies. Asthma patients (age 12 - 18 years) were invited to participated, based on medication refill records. The main study outcome was medication adherence, measured with the Medication Adherence Report Scale (MARS). Secondary outcomes were asthma control and quality of life. Outcomes were measured at start (t=0 months) and at the end of follow-up (t=6 months). Mixed-effects models were used to analyze the effect.

Results: In total, 234 adolescents (147 in the control group and 87 in the intervention group) completed the study; mean age 15.1 ± 1.9 years and 52.6% females. Self-reported adherence rates of patients with low baseline adherence (MARS scores ≤19; n=76) increased with 1.42 points in the intervention group (n=26), whereas the rates of patients in the control group (n=50) decreased with 0.70 points (intervention effect +2.12, p=0.04). This effect was stronger (+2.52, p=0.02) in non-adherent adolescents with uncontrolled asthma (n=181). No effect of the intervention was observed on asthma control or quality of life.

Conclusions: The ADAPT intervention increases adherence in adolescents with asthma having poor adherence rates. Healthcare providers should consider a tailored mHealth approach to improve the asthma treatment.

INTRODUCTION

Poor inhaled corticosteroid (ICS) adherence is common, i.e. only 22% to 63% of the asthma patients is adherent.[1] These poor adherence rates results in poorly controlled asthma and thereby an increased risk of exacerbations, healthcare utilisation, rescue medication use, healthcare costs, and decreased quality of life.[1-4] To reach sufficient asthma control, asthma patients should adhere to the prescribed medication regimen. However, previous research has shown that adherence rates further decrease during adolescence.[2] It is therefore important to develop an intervention for adolescents with asthma to increase adherence.

Medication intake behaviour is affected by multiple intentional (perceptual barriers) and unintentional (practical barriers) factors.[5,6] Adherence is particularly challenging during adolescence, because age-specific issues arise, such as a less parental supervision, social stigma, and risk factors might play a role (e.g. smoking).[5,7] Moreover, forgetting is one of the main reasons for adolescents to not take asthma medication as prescribed.[7,8] To meet the needs of adolescent patients, an adherence intervention should therefore target multiple aspects of non-adherent behaviour, i.e. overcome practical barriers, being educative and informative, motivate the patient, and ensure family or peer support.[9,10] Digital monitoring and feedback from healthcare providers has also shown to be effective in improving paediatric medication adherence.[11]

A mobile health (mHealth) intervention seems a feasible and acceptable method to support adherence in young patients, because mHealth can target different aspects of non-adherent behaviour and it has the potential to empower patients with different tools.[11,12] Moreover, almost all Dutch adolescents own a smartphone,[13] and adolescents with asthma also suggested the use of an smartphone application (app) to support their disease management.[8,14]

Many mHealth interventions to improve adherence have been developed.[15-17] However most of these were not effective, not intended for adolescents, or targeted just one aspect of non-adherent behaviour, e.g. a reminder to prevent forgetting.[18-21] Previous studies showed that solely one element is not effective in improving medication adherence in children and adolescents.[22] Therefore we developed the ADolescent Adherence Patient Tool (ADAPT).[23] This interactive mHealth intervention has been developed in accordance with adolescents with asthma, is based on the Common Sense Model of Self-Regulation, and has educational, motivational, behavioural, and self-monitoring elements.[8,23] The aim of this study was to evaluate the effectiveness of the ADAPT intervention in improving ICS adherence in adolescents with asthma. In addition, we studied the effect of the intervention on asthma control and asthma related quality of life.

MATERIAL AND METHODS

We conducted a cluster randomised controlled trial in Dutch community pharmacies affiliated with the Utrecht Pharmacy Practice network for Education and Research (UPPER).[24] Detailed rationale and design of the study have been described elsewhere.[23]

The participating pharmacies were randomly divided over the control and the intervention group. Interim analysis were performed when 42 pharmacies participated. Thereafter 24 extra pharmacies were included, and they were randomised (1:3) over the control and intervention group. Patients included in the control group received usual care consisting of inhalation instruction at a first dispensing and automated pharmacy information systems that will detect excessive bronchodilator or insufficient ICS use. Patients and pharmacists in the intervention group had six months access to the ADAPT intervention, in addition to usual care.

Patients fulfilling the following criteria were eligible for inclusion: age 12 - 18 years, filling of at least two prescriptions for ICS or a fixed combination of ICS with a long-acting beta-agonist (ICS/LABA) during the previous 12 months, and having a smartphone (iOS or Android). Patients who had insufficient comprehension of the Dutch language or were dependent on (in)formal carers to take their medication were excluded. Due to the nature of the intervention, blinding of group assignments for both patients and pharmacists was impossible.[23]

Upon receiving the signed informed consent, the first online questionnaire (baseline measurement) was sent to the patient, via e-mail. At the end of follow-up (six months), the second online questionnaire was sent (follow-up measurement).[23]

The ADAPT intervention

The ADAPT intervention consisted of a smartphone application which was securely connected to a desktop application of the patient's community pharmacy; in the Netherlands patients use generally one pharmacy to collect their medication prescriptions. The app contained different elements targeting multiple aspects of non-adherent behaviour:

- Weekly Control of Allergic Rhinitis and Asthma Test (CARAT)[25] to monitor disease control over time, both patients and pharmacists had insights in the obtained disease control score;
- Short educational and motivational movies on asthma related topics;
- Medication reminder alarm to prevent forgetting;
- Peer chat function to contact peers who participate in the study;
- Pharmacist chat function to facilitate healthcare provider contact;
- Two questions once every two weeks to monitor (the type of) non-adherence; one about forgetting (unintentional) and one about deciding to miss out a dose (intentional).

The intervention was interactive; pharmacists had the possibility to monitor the CARAT scores, to send additional movies, to change app settings, and to contact the patient. The pharmacists received a half-day training about asthma and medication use by adolescents, additionally they received on the spot instructions on the use of the ADAPT desktop application.[23]

Outcomes

The primary outcome was self-reported medication adherence, assessed with the Medication Adherence Report Scale (MARS).[26] This questionnaire consists of five questions on forgetting, changing dosage, stopping, skipping, and taking less. The total score ranges between 5 and 25, where a higher MARS score indicates higher self-reported adherence. Previous studies used a MARS cut-off score ≥23 to define adherent patients.[27,28] We conducted sensitivity analyses using different cut-offs, i.e. MARS ≥19 to MARS ≥24.

Secondary outcomes were self-reported disease control and asthma related quality of life. Disease control was assessed with the CARAT.[25] This questionnaire contains ten questions about asthma and allergic rhinitis symptoms, resulting in a score between 0 and 30, where a score >24 represents good control. For the questions regarding allergic rhinitis (questions 1 - 4), a score of >8 is sufficient, and for the asthma related questions (questions 5 - 10) ≥16 is sufficient for control. Asthma related quality of life was assessed with the Paediatric Asthma Quality of Life Questionnaire (PAQLQ).[29] This questionnaire covered three domains: symptoms, activity limitations, and emotional function. All domains were scored between 1 and 7, where seven indicates the highest quality of life. All outcomes were measured at baseline (t=0 months) and at the end of follow-up (t=6 months).

Statistical analysis

The trial was designed with a planned sample size of 352 patients, to detect a relevant difference (1.5 ± 4.0) in MARS scores with a power of 80%, a significance level of 95%, accounting for 35% dropout, and corrected for the cluster randomised design.[23] Interim analysis showed sufficient power for the current number of participants divided over more pharmacies.

To compare the groups at baseline we used a mixed-effects model, chi-squared test, or fisher's exact test, depending on the type of variable. The effect of the intervention on the primary and secondary study outcomes was analyzed using mixed-effects models, to correct for the cluster design. As post-hoc analysis, we checked for interactions between the intervention effect and baseline scores, performed sensitivity analysis to find the significant cut-off value for adherence, and stratified the data by age, gender, adherence, and asthma control. A generalized linear mixed-effects model was used for the binomial variables. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. Statistical analyses were performed using R (version 3.4.3) packages '*glmm*', '*lme4*', and '*nlme*'. P-values <0.05 were considered statistically significant.

Ethics and confidentially

The ADAPT study was approved by the Medical Review Ethics Committee of the University Medical Centre Utrecht (NL50997.041.14) and by the Institutional Review Board of UPPER,[24] Department of Pharmaceutical Sciences, Utrecht University. All patients had to complete informed consent before start of the study, and for patients younger than 16 years both parents also had to sign. The trial is registered in the Dutch Trial Register (NTR5061). Personal data was encrypted, using a code consisting of a pharmacy and patient number, to ensure privacy.

RESULTS

Descriptive statistics

A total of 1,204 adolescents with asthma were invited from 66 community pharmacies between July 2015 and May 2016. In total, 253 adolescents (21%) agreed to participate (0 - 13 patients per pharmacy) and 234 adolescents completed the study (***Figure 1***). Main reasons for not willing to participate were a lack of interest or not taking daily asthma medication anymore. Data collection was finished in July 2017. Baseline characteristics of the study population are presented in ***Table 1***: half of the patients was female (n=123; 52.6%), the mean age was 15.1 ± 1.9 years, and most had a Dutch ethnicity (n=207; 88.5%).

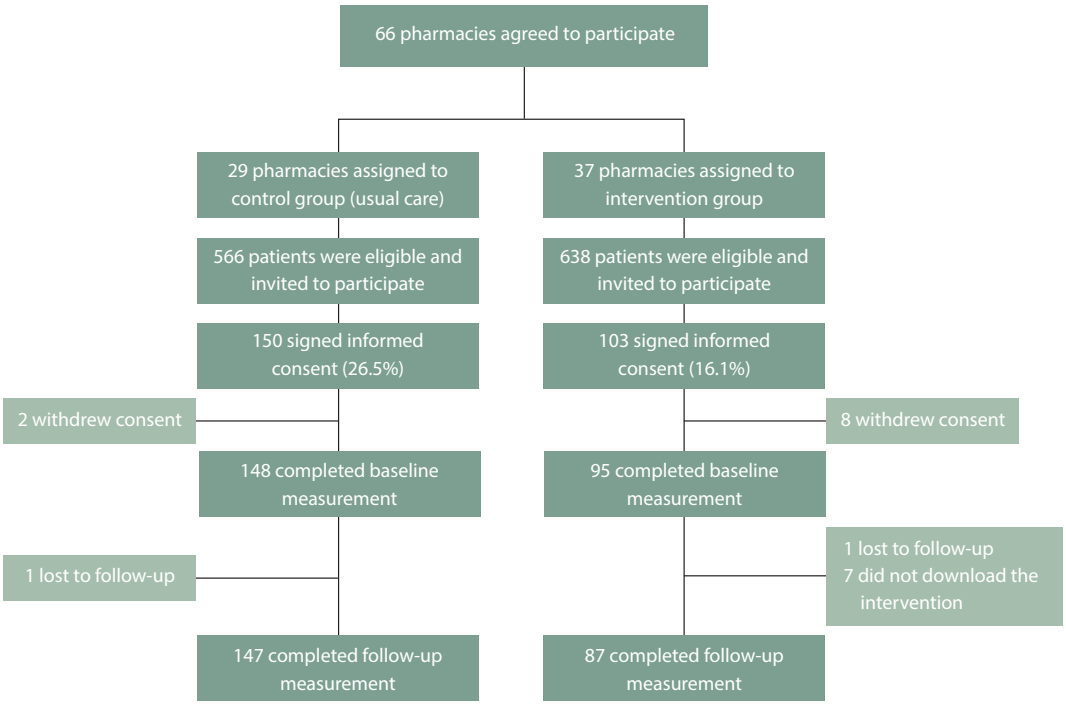


Figure 1. The ADolescent Adherence Patient Tool (ADAPT) study procedure, including randomisation, eligibility, and follow-up.

Table 1. Baseline characteristics of the study participants*

	Control (N=147) n (%)	Intervention (N=87) n (%)
Female gender	**75 (51.0)**	**48 (55.2)**
Age, mean (SD)	**15.2 (1.9)**	**15.0 (2.0)**
Native Dutch origin	**143 (97.3)**	**86 (98.9)**
Education		
Elementary school	5 (3.4)	4 (4.6)
High school: vocational level	40 (27.3)	18 (20.7)
High school: pre-university level	78 (53.0)	51 (58.6)
Vocational education	14 (9.5)	12 (13.8)
Professional education	9 (6.1)	1 (1.1)
Other	1 (0.7)	1 (1.1)
Living environment		
Urban	63 (42.9)	44 (50.6)
Village	77 (52.4)	42 (48.3)
Other (in between)	7 (4.7)	1 (1.1)
Asthma medication use[a,b]		
SABA	106 (72.1)	67 (77.0)
ICS	82 (55.8)	55 (63.2)
LABA	7 (4.8)	1 (1.1)
ICS/LABA	63 (42.9)	36 (41.4)
Other asthma medication use[b]		
Anti-allergic	9 (6.1)	6 (6.9)
Antibiotics	23 (15.6)	12 (13.8)
Montelukast	10 (6.8)	11 (12.6)
Oral corticosteroids	6 (4.1)	4 (4.6)
Other	2 (1.4)	1 (1.1)
Healthcare use[b]		
Visit asthma related doctor[c]	99 (67.3)	57 (65.5)
Self-reported health status		
Good to excellent	129 (87.8)	73 (83.9)
Bad to moderate	18 (12.2)	14 (16.1)

* No significant differences (p>0.05) between the two groups.
[a] Inclusion criteria were the collection of at least two prescriptions for ICS or ICS/LABA in the preceding year. Patients could use more than one type of medication. Four patients reported no medication use in the previous six months.
[b] Self-reported data on the previous six months.
[c] General practitioner, paediatrician, pulmonologist, pulmonary nurse, physiotherapist, first aid, and/or alternative doctors.

ICS, inhaled corticosteroids; ICS/LABA, inhaled corticosteroids in a fixed combination with a long-acting beta-agonist; LABA, long-acting beta-agonist; SABA, short-acting beta-agonist; SD, standard deviation.

Primary outcome

No effect of the intervention was observed on the MARS score (p=0.25; ***Table 2***). However there was an interaction between MARS baseline and follow-up (p=0.02). Subsequently, adherence rates of patients with low baseline adherence (n=76; MARS ≤19) increased with 1.42 points in the intervention group (n=26), whereas it decreased with 0.70 points in the control group (n=50), ***Figure 2a***. Thus we observed an intervention effect of +2.12 on the MARS score (p=0.04). This intervention effect on the mean MARS score was stronger (+2.52, p=0.02) in uncontrolled patients (n=181; CARAT ≤24), ***Figure 2b.*** The MARS cut-off scores were based on the best statistical fit.

When using the MARS cut-off (MARS ≥23) as an indicator for sufficient adherence, there was no effect of the intervention in improving adherence; OR 1.07 [CI 0.54; 2.20]. Sensitivity analysis (MARS ≥19 to ≥24) also showed no effect of the intervention (results not shown). At baseline, 40.1% (n=59) of the control group and 33.3% (n=29) of the intervention group were adherent based on the MARS cut-off (MARS ≥23). At the end of follow-up, this percentage was decreased in the control group to 38.8% (n=57) and increased in the intervention group to 36.8% (n=32).

Table 2. Mean outcomes (with standard deviation) and the intervention effect on the validated outcome measurements

	Control (N=147)		Intervention (N=87)		Intervention effect	
	Baseline	**Follow-up**	**Baseline**	**Follow-up**	**p-value[a]**	**Effect size (95% CI)**
Medication Adherence Report Scale (MARS)						
Total	20.4 (4.0)	19.3 (5.1)	20.4 (3.9)	19.9 (4.0)	**0.25**	+0.60 (-0.43; 1.63)
Control of Allergic Rhinitis and Asthma Test (CARAT)						
Total	19.8 (5.6)	20.9 (5.1)	19.3 (5.3)	20.7 (5.2)	**0.81**	+0.13 (-0.95; 1.22)
Allergic rhinitis	7.1 (3.1)	7.6 (2.7)	7.3 (3.2)	7.6 (2.8)	**0.78**	-0.10 (-0.82; 0.62)
Asthma	12.7 (3.8)	13.3 (3.4)	12.1 (3.2)	13.1 (3.5)	**0.51**	+0.23 (-0.47; 0.93)
Paediatric Asthma Quality of Life Questionnaire (PAQLQ)						
Total	6.0 (1.0)	6.1 (0.9)	5.8 (0.9)	6.0 (0.8)	**0.71**	+0.03 (-0.13; 0.20)
Symptoms	5.7 (1.2)	6.0 (1.0)	5.6 (1.0)	5.9 (1.0)	**0.71**	-0.04 (-0.25; 0.17)
Activity limitation	5.5 (1.1)	5.6 (1.0)	5.2 (1.2)	5.6 (1.1)	**0.34**	+0.11 (-0.12; 0.34)
Emotional function	6.5 (0.8)	6.6 (0.8)	6.4 (0.9)	6.5 (0.8)	**0.55**	+0.05 (-0.11; 0.21)

[a] Calculated with mixed-effects model.
CI, confidence interval.

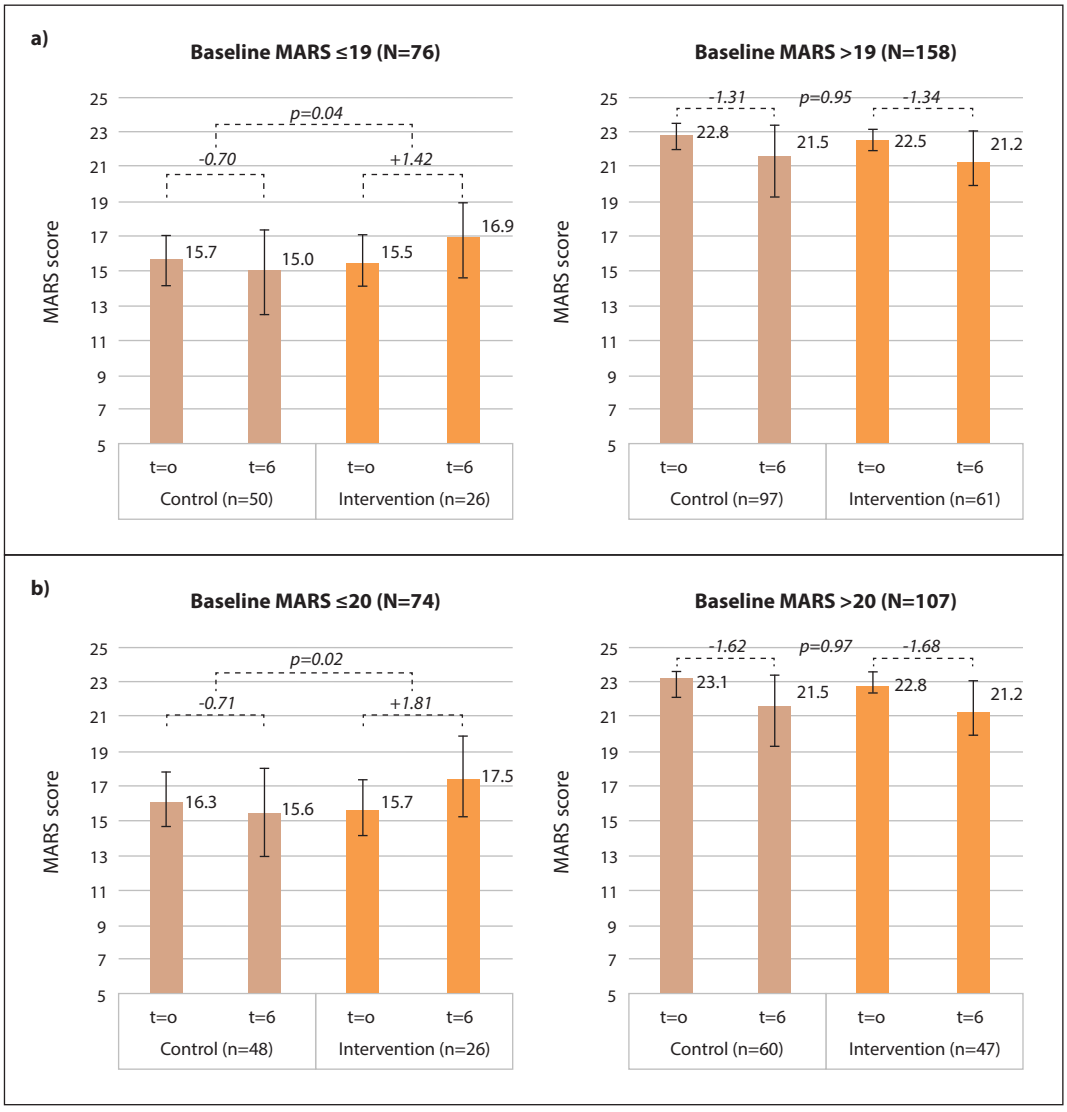


Figure 2a. The mean Medication Adherence Report Scale (MARS) score at start (t=0) and end of follow-up (t=6) of 234 patients with low adherence (left) or high adherence rates (right) per group.
Figure 2b. The mean Medication Adherence Report Scale (MARS) score at start (t=0) and end of follow-up (t=6) of 181 uncontrolled patients (Control of Allergic Rhinitis and Asthma Test ≤24) with low adherence (left) or high adherence rates (right) per group.

Secondary outcomes

No intervention effect was observed on disease control, as measured with the CARAT (p>0.05; ***Table 2***). In total, 26.5% (n=39) of the control group and 16.1% (n=14) of the intervention group had control over their symptoms at baseline (CARAT >24). This proportion remained the same in the control group and increased in the intervention group to 23.0% (n=20). The effect of the intervention

in patients with uncontrolled symptoms (CARAT ≤24) was 1.56, versus 0.71 for controlled patients (CARAT >24), however this opposite effect was not significantly different; OR 1.23 [CI 0.56; 2.77].

The number of patients with sufficient asthma control (CARAT questions 5 - 10; score ≥16) differed between the groups at baseline; 26.5% (n=39) control group and 13.8% (n=12) intervention group (p=0.02). The percentage of patients with sufficient asthma control increased in both groups, to 29.3% (n=43) in the control group and 29.9% (n=26) in the intervention group. However no intervention effect was observed on the CARAT asthma score (p=0.51; ***Table 2***). Additionally, no intervention effects were observed on the Paediatric Asthma Quality of Life Questionnaire (PAQLQ) scores (p>0.05; ***Table 2***).

Stratifying the data by age, gender, median MARS score, and median CARAT score did not affect the results (results not shown), thus no intervention effect was found.

Patient profile

The baseline characteristics of the study population for which the intervention was effective (MARS ≤19; n=76) are shown in ***Table 3***. These patients were on average 0.7 years older (p=0.02) and had lower disease control (p=0.01) compared to adolescents with high baseline adherence rates. Within the low adherent patients, the CARAT total score and CARAT allergic rhinitis score increased with respectively 1.9 (p=0.02) and 1.1 (p=0.01). Within the high adherent patients (n=158), the CARAT asthma score and the PAQLQ symptom score increased with respectively 0.8 (p=0.04) and 0.2 (p=0.046). However, within both groups no intervention effect was found on disease control and asthma related quality of life (p>0.05).

More than half of the non-adherent patients (n=65; 85.5%) had no disease control (CARAT ≤24). At the end of follow-up, almost all of these patients (n=59; 90.7%) remained uncontrolled and six participants improved their control (9.2%). The percentage of uncontrolled patients in the adherent group was 73.4% (n=116), and 13.8% (n=16) of those patients improved their control. No differences in the percentage of uncontrolled asthma patients were observed within and between the adherence groups (p>0.05).

Table 3. Patient baseline characteristics per adherent subgroup: low adherent (MARS ≤19) and high adherent (MARS >19).

	Low adherent (N=76), n(%)	High adherent (N=158), n(%)	p-value[a]
MARS, mean (SD)	15.6 (3.1); range 7 - 19	22.7 (1.5); range 20 - 25	*NA*
Female gender	41 (54.0)	82 (52.0)	0.88
Age, mean (SD)	15.6 (2.0)	14.9 (1.8)	**0.02**
Asthma medication use			
SABA	56 (73.7)	117 (74.1)	1.00
ICS	45 (59.2)	92 (58.2)	1.00
LABA	2 (2.6)	6 (3.8)	0.94
ICS/LABA	30 (39.5)	69 (43.7)	0.51
Other asthma medication use			
Anti-allergic	5 (6.6)	10 (6.3)	0.94
Antibiotics	8 (10.5)	27 (17.1)	0.23
Montelukast	4 (5.3)	17 (10.8)	0.17
Oral corticosteroids	2 (2.6)	8 (5.1)	0.06
Other	1 (1.3)	2 (1.3)	0.98
Healthcare use			
Visit asthma related doctor	47 (61.8)	109 (69.0)	0.28
Self-reported health status			
Good to excellent	65 (85.5)	137 (86.7)	0.18
Bad to moderate	11 (14.5)	21 (13.3)	
Control of Allergic Rhinitis and Asthma Test (CARAT)			
Total, mean (SD)	18.2 (5.7); range 0 - 28	20.3 (5.3); range 4 - 30	**0.01**
Allergic rhinitis, mean (SD)	6.4 (3.4); range 0 - 12	7.5 (3.0); range 1 - 12	**0.01**
Asthma, mean (SD)	11.8 (3.5); range 0 - 18	12.8 (3.6); range 0 - 18	**0.04**
Paediatric Asthma Quality of Life Questionnaire (PAQLQ)			
Total	5.8 (1.0)	5.9 (0.9)	0.20
Symptoms	5.5 (1.2)	5.8 (1.1)	0.10
Activity limitation	5.3 (1.2)	5.4 (1.1)	0.35
Emotional function	6.4 (1.0)	6.5 (0.8)	0.60

[a] P-value represents the difference between the groups.
ICS, inhaled corticosteroids; ICS/LABA, inhaled corticosteroids in a fixed combination with a long-acting beta-agonist; LABA, long-acting beta-agonist; MARS, Medication Adherence Report Scale; SABA, short-acting beta-agonist; SD, standard deviation.

DISCUSSION

The interactive ADAPT mHealth intervention improved adherence of adolescents with asthma having poor adherence rates. These patients were older and had less control over their symptoms, compared to the patients with high adherence rates. We did not find an intervention effect in improving adherence in the total study population. Asthma related quality of life and disease control were also not affected by the ADAPT intervention.

Within patients with high adherence rates (MARS >19, n=158) there was no effect of the intervention, although less can be achieved in patients with high adherence. These patients also had significant better asthma control, which is in line with previous studies where asthma adherence was related to better asthma control.[4,30] However, still 73.4% of these adherent patients had no control over their disease (CARAT ≤24). This emphasizes the complex relation between adherence and asthma control. Factors such as life style, medication(dosing), and inhaler technique also affect asthma control, and were not taken into account in the current study.[30] For some patients, there is also a transition of asthma symptoms during adolescence, which might affect the relation between adherence and asthma control.[31]

No intervention effects were found on asthma related quality of life, while one would expect a relation between adherence, asthma control, and quality of life. Previous research showed an association between asthma control and quality of life of adolescents in a five-year period, thus our study period might be too short to find an effect on asthma related quality of life.[32] Additionally, our study population reported high baseline quality of life and the majority had a good to excellent health status, thus there was less to achieve.

We showed the effectiveness of an interactive mHealth intervention in patients having poor medication adherence; there was an increase of 1.5 on a MARS scale ranging between 5 to 25. Although it was small, it was significant effect, however the clinical relevance is debatable. More research is therefore needed towards this effect, and the intervention should be tailored to patients who need it most (i.e. non-adherent patients). A baseline adherence measurement (before using mHealth) might be an useful tool to personalise the treatment, i.e. recommend the use of the mHealth intervention, or not.

The current study used pharmacists as the healthcare provider, because pharmacists are increasingly expected to support appropriate use of medication in integrated care settings.[33] Increased collaboration between pharmacists and physicians may facilitate the identification of uncontrolled patients with low adherence rates. Pharmacists can subsequently support these patients with their medication use, by implementing mHealth interventions.

The aim of our study was to increase adherence in adolescents with asthma. We selected patients based on filling of at least two prescriptions for ICS or ICS/LABA during the previous 12 months. Mulder *et al.* 2016 showed that this is a reliable proxy for an asthma diagnosis.[34] Moreover, we checked the asthma diagnosis of the participants in the questionnaire. It was hard to include sufficient adolescents, therefore we recruited extra pharmacies, and we also asked for reasons why patients did not want to participate; a lack of interest and not taking daily asthma medication anymore were mostly mentioned. Previous studies confirmed that it is extra difficult to motivate adolescents for healthcare interventions, because adolescents do not want to be different from their healthy peers.[5,35] Moreover, some children with asthma lose their symptoms during adolescence.[31]

Thus adolescents require special attention due to their development, and due to the course of their asthma symptoms (which can affect adherence).[5]

Many previous studies focused on mHealth interventions for chronic diseases,[12,14,18,19,22] findings of those studies were incorporated in the development of our intervention. For example, the ADAPT intervention was developed in close collaboration with adolescents with asthma and healthcare providers, was based on a theoretical framework, was interactive, and contained multiple elements to target different aspects of non-adherent behaviour. This combination makes the ADAPT intervention distinctive from previous asthma mHealth interventions.[18,22] Moreover, the elements of the ADAPT intervention contributed to shared decision making, and to blended care, where integrated face-to-face contact is alternated with online information. A strength of our study was the large number of participants in combination with the low drop-out rate, which is rarely seen in mHealth studies, or studies concerning adolescents.[11]

There are also several limitations of the study, such as a response bias, as motivated patients are more interested in participating and more willing to use the ADAPT intervention (intervention arm). However, at baseline, 37.6% adolescents (n=88) were adherent and 22.1% adolescents (n=51) had control over their symptoms. This finding does not support that only highly motivated patients participated.

Another limitation might be the use of self-reported measurements, resulting in a potential desirability bias. Adherence could also be measured by using refill records. However our study period covered six months, and in the Netherlands patients collect chronic medication once every three months. It was therefore not possible to calculate adherence rates during the study period based on refill records. Moreover, quality of life can only be measured by self-report, therefore we used the PAQLQ questionnaire, which is designed for young people with asthma.[36] We used the CARAT to measure disease control, because the CARAT is a validated instrument for Dutch adolescents, which distinguishes between asthma and allergic rhinitis symptoms.[37] Moreover, the CARAT is less invasive than direct measurements and therefore more convenient and accessible for this age-group.

CONCLUSIONS

An interactive mHealth intervention, such as ADAPT, resulted in significantly higher adherence rates in adolescents with asthma having poor adherence rates. Based on this study, healthcare providers should consider a tailored mHealth approach in the treatment of adolescents with asthma. Future studies should focus on the long-term effects, the intervention use, and the implementation and integration possibilities of a mHealth intervention in clinical practice.

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CHAPTER 4.3

Effective engagement of adolescent asthma patients with mHealth supporting medication adherence

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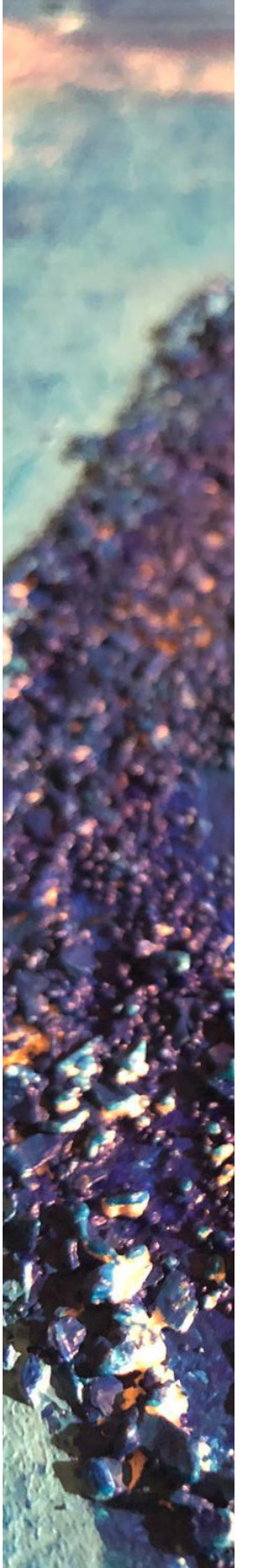

ABSTRACT

Background: Mobile health (mHealth) applications have the potential to support patient's medication use and are therefore increasingly used. Applications with broad functionality are suggested to be more effective, however not much is known about the actual use of different functionalities and the effective engagement.

Objectives: The aim of this study was to explore the use and the effective engagement of adolescents (age 12 - 18 years) with the ADolescent Adherence Patient Tool (ADAPT).

Methods: The ADAPT intervention consisted of an application (app) for patients connected to a management system for their pharmacist. The aim of the ADAPT intervention was to improve medication adherence and therefore the app contained multiple functionalities: questionnaires to monitor symptoms and adherence, a medication reminder, short movies, a pharmacist chat, and a peer chat. For this study, data of the ADAPT study, a cluster randomised controlled trial, was used. Adolescents with asthma had six months access to the ADAPT intervention and all app usage was securely registered in a log file.

Results: In total, 86 adolescents (age 15.0 ± 2.0 years) used the ADAPT app for 17 times (range 1 - 113) per person. Females used the app more often than males (p=0.01) and for a longer period of time (p=0.03). On average three different functionalities were used, and 13% of the adolescents used all functionalities of the app. The questionnaires to monitor symptoms and adherence were used by most adolescents. The total app use did not affect adherence, however activity in the pharmacist chat positively affected medication adherence (p=0.03), in particular if patients sent messages to their pharmacist (p=0.01).

Conclusions: MHealth applications for adolescents with asthma should contain different functionalities, in order to serve the diverging needs and preferences of individual patients. Suggested key functionalities to promote use and effectiveness in adolescents with asthma are questionnaires to monitor symptoms and a healthcare provider chat.

INTRODUCTION

Mobile health (mHealth) interventions have the potential to support patients with their medication use and are therefore increasingly used.[1-4] Patients highly appreciate those type of interventions, mainly because of the high usability, feasibility, and acceptability of mHealth.[5] However, the evidence for efficacy of mHealth for chronic patients is limited, except for moderate quality evidence of improvement in asthma patients.[3]

MHealth seems in particular promising for specific patient groups such as adolescents, because almost all adolescents own a smartphone (95%), they widely use their phone for social networking, and they are generally poor adherent.[6,7] However, until now not many mHealth interventions are developed for adolescents, while mHealth interventions for adolescents were rated as feasible and acceptable with modest evidence for their efficacy in improving adherence.[8-10] Therefore, we developed the ADolescent Adherence Patient Tool (ADAPT), an interactive mHealth intervention to improve medication adherence in adolescents with asthma. A patient centred approach and a theoretical framework were used to develop this intervention.[11] As a result, the intervention consisted of a smartphone application (app) for patients, which was connected to a desktop application for pharmacists, enabling communication between patients and healthcare providers.

Previous studies showed that multi-faceted mHealth interventions are more effective in improving medication adherence than interventions targeting only one aspect of non-adherent behaviour,[4,12-14] because medication adherence is a complex behaviour affected by many factors.[15] Accordingly, the ADAPT intervention contained multiple functionalities to support medication adherence; questionnaires to monitor symptoms and adherence, a medication reminder, short movies, a pharmacist chat, and a peer chat.[11] We evaluated the ADAPT intervention in a cluster randomised controlled trial and adherence improved significantly in adolescents with asthma having poor adherence rates.[16]

Besides the efficacy of mHealth, it is important to study the actual use of mHealth interventions. Currently little is known about the actual use of mHealth applications by adolescents with asthma. Moreover it is important to identify the association between the use of different mHealth functionalities and the effect on the intended outcome, also known as the 'effective engagement'. This will provide directions for other mHealth interventions aiming to improve adherence, as there is still limited evidence for the efficacy of mHealth.[17,18] Therefore the aim of the current study was to explore the use of the ADAPT app, a complex adherence mHealth intervention, by adolescent with asthma, and to study the effective engagement of patients with the ADAPT app.

METHODS

Data collection

Data of the ADAPT study, a cluster randomised controlled trial, was used. The aim of the ADAPT study was to evaluate the effect of the ADAPT intervention on adherence, measured with the Medication Adherence Report Scale (MARS).[19] The complete ADAPT study protocol and effectiveness of the mHealth intervention have been described elsewhere (***Chapter 4.1*** and ***Chapter 4.2***).[11,16] Briefly, adolescents with asthma (age 12 - 18 years) who were in the possession of a smartphone were eligible for participation. In total, 638 patients were invited for the intervention group and 103 (16.1%) signed informed consent. There was a 16% drop-out rate (n=8 withdrew consent, n=7 did not download the app, and n=1 was lost to follow-up), resulting in 87 patients and 27 pharmacists, who had six months access to the ADAPT intervention. The control group consisted of 147 patients and 27 pharmacists (data not shown).

We asked patients in the intervention group (N=87) to use the app at least once a week; they received a weekly push notification. After six months upon completing the study, patients received a gift card (regardless their app usage). All ADAPT app use was securely registered in a log file, i.e. a document with an automatic produced and time-stamped documentation of events.

ADAPT intervention

The ADAPT app (***Figure 1***) was connected to a desktop application of the patient's own community pharmacist.[11] The different functionalities of the app are described below.

- ***Questionnaire to monitor symptoms***

Patients received a weekly push notification (26 times in total) to complete the Control of Allergic Rhinitis and Asthma Test (CARAT) to monitor their symptoms.[20] This validated questionnaire consisted of ten questions where a total score between 0 and 30 could be obtained (>24 indicated good disease control). The total score could be divided into two sub scores: allergic rhinitis score (items 1 - 4, score >8 indicated good control) and asthma score (items 5 - 10, score ≥16 indicated good control). Patients had access to their obtained CARAT scores in the ADAPT app and received textual feedback about their results. The CARAT scores were also sent to the pharmacist's desktop application and pharmacists received e-mail notifications when patients had no disease control (CARAT score ≤24).

- ***Medication alarm***

Patients could set a medication alarm to prevent forgetting. The alarm was adjustable to the patient's preference, i.e. patients could set the alarm once or twice a day at their preferred time. The alarm was not connected to their inhaler medication, thus it did not register if medication was already taken. Unfortunately, use of the medication alarm was not registered in the log file, as the alarm settings were saved locally.

- ***Short movies***

Almost every week a short movie about an asthma-related topic (e.g. lifestyle, medication use, friends) became visible in the app, to educate and motivate the patient. Patients did not receive a push notification, although in the app a notification was visible when a new movie became available. In total, 21 movies became available during the six months study period. Pharmacists had access to the movie database and could sent additional movies based on the patient's needs, for example, about inhaler techniques.

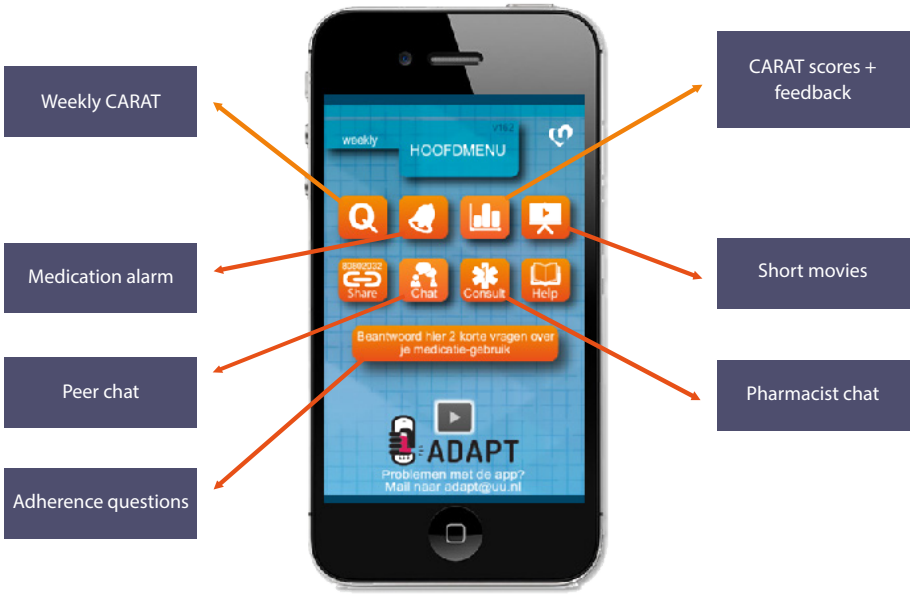

Figure 1. The ADolescent Adherence Patient Tool (ADAPT) with the different functionalities.
CARAT, Control of Allergic Rhinitis and Asthma Test.

- ***Peer chat***

The peer chat gave patients the opportunity to share experiences and discuss asthma related topics with other participants. This was an age-specific functionality, as peers are important during adolescence.[21] Adolescents recommended this functionality during the developmental phase.[31] The messages were divided in six topics: asthma, general, going out, pets, sports, and other. There was no moderator involved as we did not want to disrupt the interaction between adolescent peers.

- ***Pharmacist chat***

The pharmacist chat facilitated direct contact between the adolescent and their pharmacist, which is important because adolescents are not often seen in the pharmacy.[22] Pharmacists voluntary signed up for the ADAPT study and were randomised to the intervention group. Pharmacists could

contact their 'own' patients via the intervention, as in the Netherlands every patient is registered at one pharmacy and mostly fill all their prescriptions there. Pharmacists received e-mail notifications when patients sent a message. The aim of this functionality was to educate and motivate patients.

- ***Adherence questions***

Once every two weeks (14 times in total) two questions concerning adherence appeared in the app. The questions were based on items of the MARS. The first question was related to unintentional non-adherence *"How often did you forget to take your medication in the previous week?"* and the other was related to intentional non-adherence *"How often did you decided to miss out a dose in the previous week?"*. Patients could answer these questions using a five-point Likert scale ranging from 1 (always) to 5 (never).

Data analysis

Descriptive statistics of all variables were calculated. For skewed data, the median with interquartile range (IQR) is shown instead of the mean with standard deviation. We divided the adolescents in three groups based on the frequency of app usage during the six months study period: low (≤10), average (>10 and ≤25), and high (>25) frequent users. All log file data were converted to Excel and thereafter statistical analyses were performed using R (version 3.4.3) packages '*nlme*' and '*lme4*'. P-values <0.05 were considered statistically significant.

Effective engagement

We used (generalized) linear mixed-effects models to evaluate the effective engagement of adolescents and to compare groups. The 27 pharmacies of the ADAPT study (clusters) were used as random effects in the models.

Ethics and confidentially

The ADAPT study was approved by the Medical Review Ethics Committee of the University Medical Centre Utrecht (NL50997.041.14) and by the Institutional Review Board of Utrecht Pharmacy Practice network for Education and Research (UPPER), Department of Pharmaceutical Sciences, Utrecht University.[23] All participants had to sign informed consent before start of the study, for patients younger than 16 years both parents also had to sign. The trial is registered in the Dutch Trial Register (NTR5061). All (personal) app data were encrypted using 128-bits Advanced Encryption Standard (AES) and were securely saved using Hyper Text Transfer Protocol with a Secure Sockets Layer (HTTPS with SSL certificate).

RESULTS

In total, 87 adolescents (mean age 15.0 ± 2.0 years; 55.2% females) downloaded the ADAPT app on their smartphone (***Table 1***), of which 86 adolescents used it for 1,975 times between October 2015

and April 2017. The median app use per person was 17 times (IQR 6 - 31; range 1 - 113) within a period of five months (IQR 3 - 6; range 0 - 8). Females used the app more often than males (median 20.5 versus 11; p=0.01) and for a longer time (median 5 versus 6 months; p=0.03).

Table 1. Descriptives of the adolescent app users and the differences between the frequency groups

	Total (N=87) Mean (SD)	Low [b] (n=27) Mean (SD)	Average [b] (n=34) Mean (SD)	High [b] (n=26) Mean (SD)	p-values[c]		
					Low vs. average	Low vs. high	High vs. Average
Female, n (%)	**48 (55.2)**	**12 (44.4)**	**17 (50.0)**	**19 (73.1)**	0.59	**0.04**	0.08
Age	**15.0 (2.0)**	**15.4 (2.0)**	**15 (2.0)**	**14.6 (2.1)**	0.50	0.16	0.40
Adherence (MARS)	**20.4 (3.9)**	**19.3 (3.9)**	**21.4 (3.5)**	**20.3 (4.2)**	**0.04**	0.30	0.35
Disease control (CARAT)	**19.3 (5.3)**	**18.7 (6.0)**	**19.6 (5.4)**	**19.5 (4.6)**	0.52	0.72	0.80
Allergic Rhinitis	7.3 (3.2)	7.0 (3.5)	7.6 (3.1)	7.0 (3.2)	0.48	0.98	0.47
Asthma	12.1 (3.2)	11.7 (3.6)	12.1 (3.1)	12.4 (2.8)	0.68	0.47	0.72
Duration app use (months)	**4.2 (2.1)**	**3.0 (2.4)**	**4.7 (1.6)**	**6.1 (1.3)**	**<0.001**	**<0.001**	**0.008**
Frequency app use	**22.5 (22.0)**	**4.3 (2.6)**	**17.1 (4.6)**	**48.6 (22.9)**	**<0.001**	**<0.001**	**<0.001**
CARAT, n (%)[a]	85 (97.7)	25 (92.6)	34 (100)	26 (100)	*NA*	*NA*	*NA*
Adherence, n (%)[a]	72 (82.8)	15 (55.6)	31 (91.2)	26 (100)	**0.003**	*NA*	*NA*
Short movies, n (%)[a]	44 (50.6)	7 (25.9)	17 (50.0)	20 (76.9)	0.06	**<0.001**	**0.04**
Pharmacist chat, n (%)[a]	38 (43.7)	2 (7.4)	15 (44.1)	21 (80.8)	**0.006**	**<0.001**	**0.009**
Peer chat, n (%)[a]	18 (20.7)	0 (0)	7 (2.9)	11 (42.3)	*NA*	*NA*	**0.04**

[a] User: used at least once.

[b] Frequency of app use; **low:** used the app ≤10 times; **average:** used the app >10 and ≤25 times; **high:** used the app >25 times.

[c] P-values derived from (generalized) linear mixed-effects models.

App, application; CARAT, Control of Allergic Rhinitis and Asthma Test; MARS, Medication Adherence Report Scale; NA, not applicable; SD, standard deviation; vs, versus.

The exact use per functionality is described in ***Table 1***; the CARAT questionnaire, adherence questions, and short movies were used by most adolescents. There were differences in characteristics and functionalities used between the three user groups; low, average, and frequent users (***Table 1***). The low frequency app users had lower self-reported adherence rates compared to the average group (MARS 19.3 versus 21.4; p=0.04), and the high frequency group contained more females compared to the low frequency group (73.1% versus 44.4%; p=0.04). Almost all low frequent users (n=25; 92.6%;) completed the CARAT questionnaire and more than half (n=15; 55.6%) completed the adherence questions at least once. No one sent a message in the peer chat. The majority of high frequent users sent a message to their pharmacist (n=21; 80.8%) and watched a movie (n=20; 76.9%), which differed significantly from the other groups (***Table 1***).

Adolescents used on average three different functionalities of the app (IQR 3 - 4; range 1 - 5). An overview of the combinations of different functionalities used is presented in ***Figure 2,*** showing a

wide variety in app functionality use. All five functionalities were used by 13% of the adolescents (n=11). Examples of the total app usage per person are shown in ***Appendix 1***.

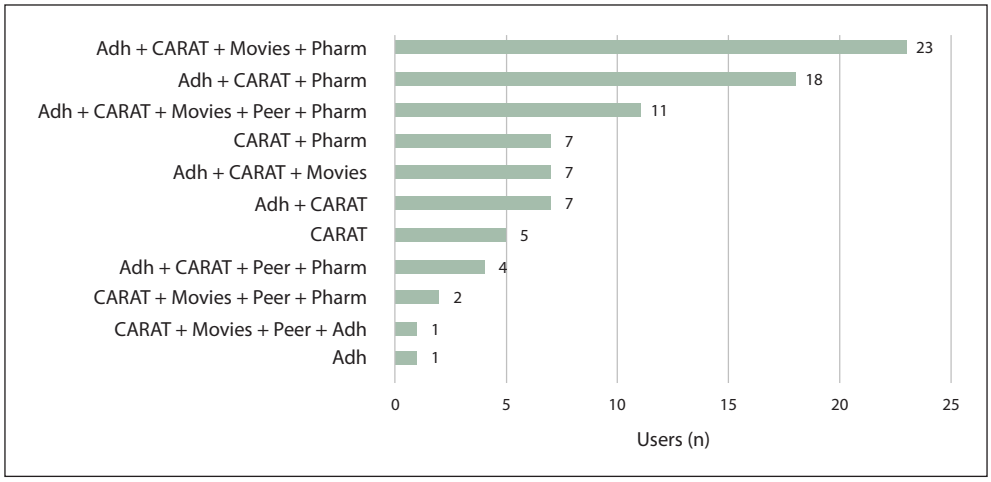

Figure 2. Overview of the combination of functionalities used by 86 adolescents.
Adh, adherence questions; CARAT, Control of Allergic Rhinitis and Asthma Test; Peer, Peer chat; Pharm, Pharmacist chat.

- ***Questionnaire to monitor symptoms***

The CARAT questionnaire is the mostly used functionality of the app; in total 1,047 questionnaires were completed by 85 (97.7%) adolescents (***Appendix 2***). Adolescents received 26 weekly reminders during the study period (six months) to complete the CARAT, however they individually completed the CARAT on average 10 times (IQR 4 - 17). There was a lot of variation between patients; range 1 - 84.

- ***Adherence questions***

The majority of adolescents (n=72; 82.8%) completed at least once the adherence questions, with a total of 221 completed questionnaires. The median of completed adherence questions per person was two (IQR 1 - 4; range 1 - 11), while the adherence questions appeared 14 times during the study period.

- ***Short movies***

Half of the adolescents (n=44; 50.6%) watched at least one movie. More females (n=29) than males (n=15) watched movies (p=0.04). In total, 21 short movies appeared in the app, however on average four different movies were watched per person (IQR 2 - 6; range 1 - 20) and each movie was seen once (IQR 1 - 1; range 1 - 4). The movies which appeared first in the app were seen most. Additionally, one pharmacist sent an additional movie with inhaler instructions to support a patient, this movie was seen twice.

- ***Pharmacist chat***

In total, 65 of the 87 adolescents (74.7%) sent and/or received three chat messages within the pharmacist chat (IQR 1 - 7; range 1 - 37) with a total of 347 messages. In most cases (53/65; 81.5%) the pharmacist started the chat, however half of those pharmacists (27/53; 50.9%) did not receive a chat message back (***Table 2***). In general, the majority of pharmacists (22/27; 81.5%) sent messages with a median of two messages per adolescent (IQR 1 - 5; range 1 - 20).

Of the 12 adolescents who started the conversation, one third (n=4) did not receive a message back (***Table 2***; reasons unknown). In total, 38 adolescents (43.7%) sent on average two messages (IQR 1 - 5; range 1 - 17) to their pharmacist, and more females (n=28) than males (n=10) sent messages to their pharmacist (p=0.004). In total, 34 conversations were held where both pharmacists and patients sent at least one message, examples are shown in ***Appendix 3***.

Table 2. Descriptives of the pharmacist chat

Pharmacists who started the chat (n=53)		
	n (%)	**No response, n (%)**
Question about the CARAT score	24 (45.3)	13 (24.5)
Welcome message	16 (30.2)	10 (18.9)
Welcome message + question	7 (13.2)	2 (3.8)
Comment on the CARAT score	4 (7.5)	1 (1.9)
Question	2 (3.8)	1 (1.9)
Patients who started the chat (n=12)		
	n (%)	**No response, n (%)**
Question about medication	5 (41.7)	3 (25.0)
Question about the app, asthma, or general	4 (33.3)	0 (0)
General comment	2 (16.7)	1 (8.3)
Medication comment	1 (8.3)	0 (0)

App, application; CARAT, Control of Allergic Rhinitis and Asthma Test.

- ***Peer chat***

The peer chat was used by 20.7% (n=18) of the adolescents, they sent in total 150 chat messages. Per adolescent 4.5 messages (IQR 3 - 11; range 2 - 29) were sent. Most messages were sent within the topics 'sports' (67 messages by 8 adolescents), 'other' (34 messages about age, school, and residence, by 6 adolescents), and 'general' (24 messages about participating in the study and the app by eight adolescents). The 18 adolescents participated in on average two topics (IQR 1 - 2; range 1 - 5). Examples of peer chat messages are shown in ***Appendix 3***.

Effective engagement

The total app use was not associated with a difference in self-reported adherence (p=0.12). Use of the CARAT questionnaire (p=0.26), adherence questions (p=0.65), short movies (p=0.80), or peer

chat (p=0.21) did also not affect the adherence outcome. However, logged activity in pharmacist chat positively affected self-reported adherence (MARS score increased with 0.1 points per message; p=0.03). Data showed that messages sent by pharmacists were not related to the outcome (p=0.06), while activity of patients in the pharmacist chat did positively affect the outcome (p=0.01), i.e. if patients sent messages to their pharmacist, it positively affected adherence (MARS score increased with 0.3 points per chat message).

DISCUSSION

Adolescents have different preferences when using a mHealth application, as there was a wide variety in app usage per person. This supports the need for multi-faceted mHealth interventions. The questionnaire to monitor symptoms was the mostly used functionality, for which they received weekly reminders. Females seemed to be more active in the ADAPT app; they used the app more often, for a longer duration, and more females sent messages to their pharmacists and watched movies. Total app use was not associated with the outcome, however sending a chat message to the pharmacist positively affected medication adherence. Based on our results, we recommend a healthcare provider chat as a key functionality for mHealth interventions to improve adherence in adolescents with asthma.

The ADAPT intervention contained a unique combination of functionalities to improve adherence and targeted a specific patient population; adolescents with asthma. We showed that the adolescents who used the app between 10 and 25 times (average users) had the highest adherence score at the start (MARS 21.4). One would expect the highest adherence score among the low frequent users, because if patients are highly adherent, they don't need the intervention, or among the high frequent users, as they are also likely to be highly adherent to the intervention use. However we did not find this, although there was no difference between adherence rates among average and high users, thus higher adherence rates might be related to more frequent app use, i.e. more adherent to the intervention.

The most used functionality was the questionnaire to monitor symptoms (***Table 1***), which was also shown in a study with adult asthma patients.[24] The symptom questionnaire provide patients (and their healthcare providers) insights in their disease symptoms over time, which should supports self-management.[25,26] Surprisingly we did not found an effect of the questionnaire use on adherence. Patient received weekly push notifications to complete the questionnaire, which might explain why this functionality was the most used functionality. However, the adherence questionnaire was the second most used functionality (***Table 1***), for which patients did not receive a push notification. The reason why most patients completed the questionnaires is unknown, i.a. curiosity might play a role. Based on all these questionnaire data (adherence and symptom control), healthcare providers could deliver personalised care to support patients, which is suggested to be more effective than usual

care.[27-30] Therefore we recommend questionnaires as an useful functionality for mHealth aimed at adolescents.

The peer chat was an age specific functionality based on the preferences of adolescents,[11,31] because peers are important for them.[32] Previous studies showed positive effects of peer led interventions for asthma patients in improving attitudes and quality of life,[33,34] and online peer support groups increased self-confidence.[35] In our study, no effects of the peer chat were found on adherence. Only 21% of the adolescents (n=18) used the peer chat, suggesting that it was not appropriate for everyone. However, the adolescents who used it, sent quite a lot of messages (eight per person). Therefore, more research is needed towards a peer chat functionality in a larger population, as more interaction is expected when more patients participate, which in its turn might support the use of the peer chat.

The pharmacist chat is a new communication method for both patients and pharmacists. It provided pharmacists with a tool to personally reach patients, which is in particular relevant for adolescent patients, as their adherence is low and they are not often seen in the pharmacy.[22] This electronic consult (e-consult) might overcome patient's barriers to approach a healthcare provider. However the current study showed that not all adolescents and pharmacists were comfortable with using this new tool, because only 44% of the adolescents (n=38) and 82% of the pharmacists (n=22) used the ADAPT pharmacist chat. Moreover, four adolescents (with different pharmacists) did not receive an answer on their question or comment (***Table 2***). For further implementation of mHealth it is important that patients always receive an answer, otherwise it will hinder further implementation.[36] Healthcare providers should therefore be stimulated and motivated to actively engage in mHealth and we suggest a back-up plan. For example, automatically personalised text messages for patients who did not receive an answer within 24 hours, or an urgent e-mail notification for pharmacists.

For further implementation of mHealth in clinical practice, it is important to study the cost-effectiveness of the ADAPT intervention. Most mHealth interventions are cost-effective,[37] however the active involvement of healthcare providers, in our case pharmacists, might negatively affect the cost-effectiveness. Thus comprehensive economic evaluations are needed,[38] to study the cost-effectiveness of the ADAPT intervention and to identify the optimal involvement of pharmacists (from an economical perspective).

Limitations

We used log data to analyze the ADAPT app usage, which a reliable method, however there are some limitations. Data used in this study are derived from a cluster randomised controlled trial, thus there might be a response bias, i.e. the participants were probably more motivated to use the intervention than the general population. However, use of the intervention still varied per person, suggesting that the mHealth use depends on patient's needs and preferences. Another limitation is that patients received a weekly reminder to complete the CARAT questionnaire, which might be a reason why the

CARAT is mostly used. Additionally, we studied the physical engagement of adolescents with the app (number of times used), while there is also psychological engagement with the intervention,[17,39] which we did not measure. The psychological engagement might also explain why patients use certain functionalities. Moreover, the generalisability of our results is limited, because our findings are based on a study among adolescents with asthma in the Netherlands. Therefore more research is needed to confirm our findings in other countries and other populations. However, the current results suggests that the possibility to chat with a healthcare provider is an important functionality for mHealth interventions aiming to increase adherence.

CONCLUSIONS

The current study showed that a complex mHealth intervention to support adherence is differently used by adolescents with asthma. The questionnaires to monitor asthma symptoms and adherence were used by most adolescents, which provided valuable data for healthcare providers and patients. Moreover, the use of the pharmacist chat positively affected adherence. These findings suggests that mHealth applications should contain different functionalities in order to serve the diverging needs and preferences of individual patients. A questionnaire to monitor symptoms and adherence and a chat with the healthcare provider are recommended key functionalities for mHealth applications for adolescents with asthma.

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We would like to thank the participating pharmacists and patients for using the intervention.

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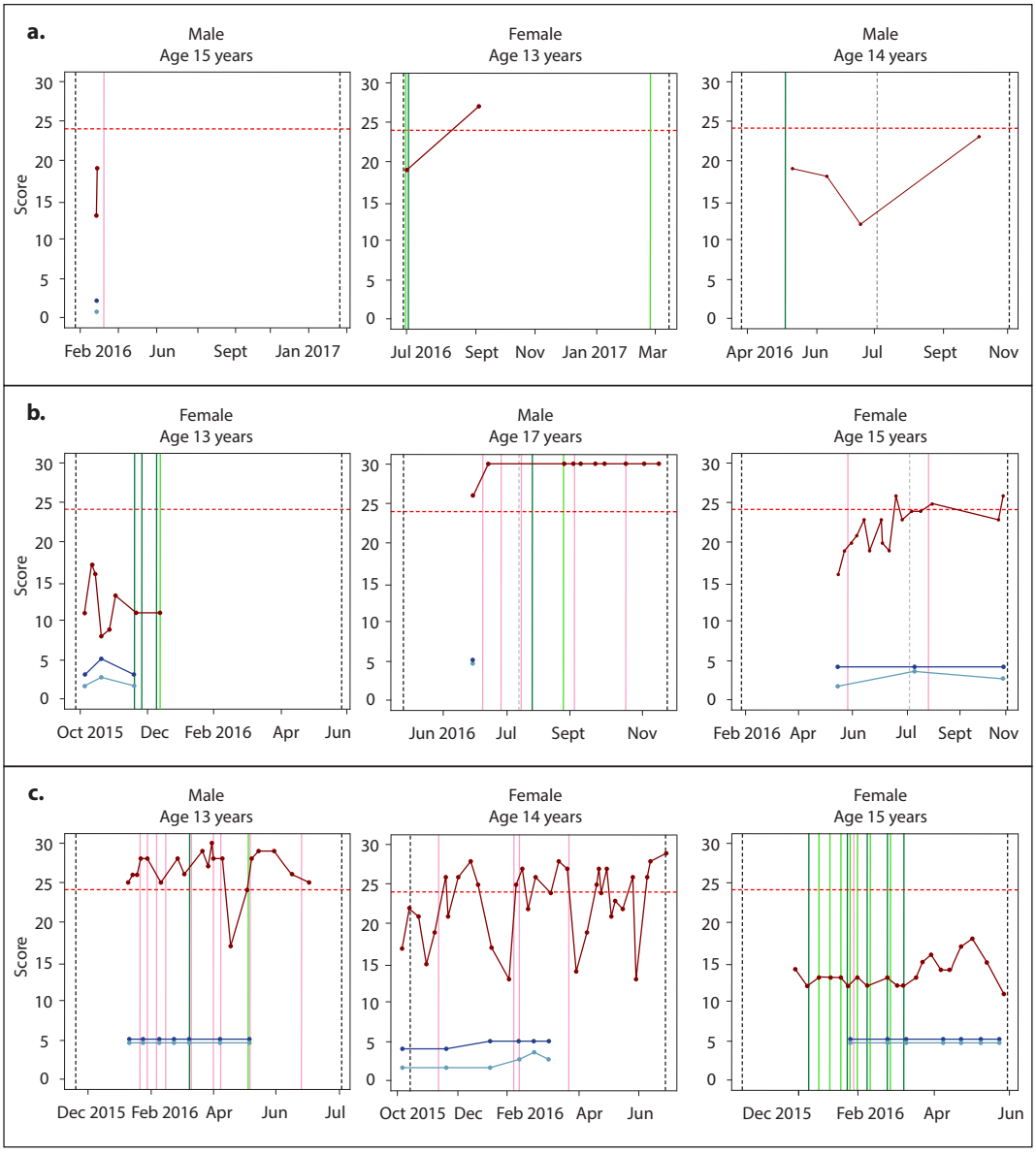


Appendix 1. Examples of mHealth application use by adolescents with asthma during the six months study period, divided in low (**1a**), average (**1b**), and high frequent (**1c**) users.

1a. Low frequent users who used the intervention for 4 (left), and 5 times (middle and right).

1b. Average frequent users who used the intervention for 17 (left), 18 (middle), and 22 times (right).

1c. High frequent users who used the intervention for 40 (left), 43 (middle), and 50 times (right).

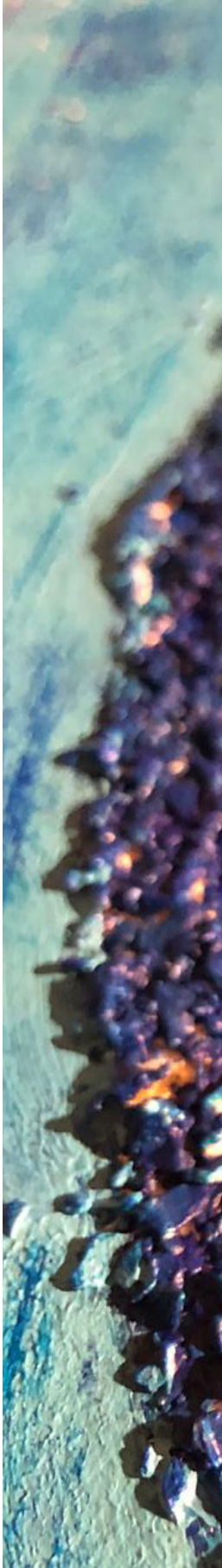
Horizontal lines: **Red:** Control of Allergic Rhinitis and Asthma Test (CARAT) score, dotted line represents the threshold (>24); **Blue:** adherence questions; **light blue:** forgot to take, **dark blue:** decided not to take (5 = never, 1 = always).

Vertical lines: **Green:** pharmacist chat; **dark green:** message sent by pharmacist; **light green:** message sent by patient; **Pink:** watched a movie; **Black:** dotted line indicates the baseline and end of follow-up date of the study; **Grey:** dotted line indicates the push notification update of the mHealth application.

Appendix 2. Overview of the 1,047 Control of Allergic Rhinitis and Asthma Test (CARAT) scores of 85 adolescents; on average 12.3 scores per person. **Blue:** Total CARAT score, dotted line represents the threshold (>24). **Green:** asthma sub score, dotted line represents the threshold (≥16). **Red:** allergic rhinitis sub score, dotted line represents the threshold (>8).

Appendix 3. Examples of chat messages sent in the ADolescent Adherence Patient Tool (ADAPT) intervention

Chat (Topic)	Sender	Message
Pharmacist chat	Female; 15 years	"Is it necessary to take the medication at a fixed time?"
	Pharmacist	"If you do not take your medication at a fixed time, you may forget to take it. Your medication will be less effective then."
Pharmacist chat	Pharmacist	"How are you? Your questionnaire scores are quite low. Is there anything I can help you with? Do you want to practice your inhaler techniques in the pharmacy?"
	Female; 18 years	"I still have a cold, but I think my inhaler technique is fine."
	Pharmacist	"How often do you take your medication?"
Peer chat (Sports)	Female; 13 years	"Do you suffer a lot when playing sports?"
	Female; 13 years	"I only suffer during endurance running, but my trainers take that into account. Although I'm not able to run the shuttle run test at school, because it is very stuffy and dusty, and I'm surrounded by many people."
Peer chat (Other)	Female; 18 years	"Does anyone have experience with hay fever tape? Can a physiotherapist do this?"



CHAPTER 5

Implementation of mHealth in the community pharmacy

CHAPTER 5.1

Evaluation of a mobile health intervention to support asthma self-management and adherence in the pharmacy

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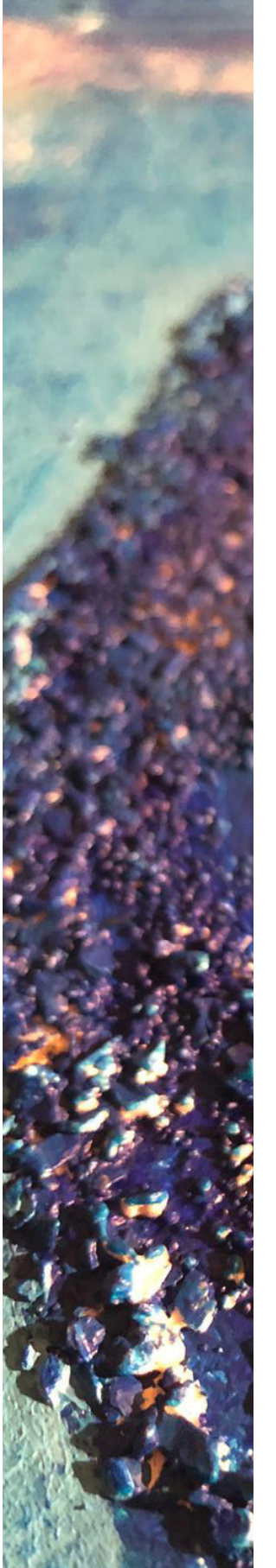

ABSTRACT

Background: Several effective mobile health (mHealth) interventions have been developed to support patients with their medication use, however hardly any is implemented in clinical practice. Process evaluations and user experiences are therefore important for further implementation.

Objective: To explore experiences, barriers, and facilitators of pharmacists and patients towards the use of the interactive ADolescent Adherence Patient Tool (ADAPT). In addition, the perceptions of pharmacists towards mHealth interventions in general were explored.

Setting: Dutch community pharmacies.

Methods: Pharmacists (N=24) and adolescents with asthma (N=87; age 12 - 18 years) completed a questionnaire about the ADAPT intervention. Pharmacists who did not have access to the ADAPT intervention (N=26) completed a questionnaire on their perceptions towards mHealth.

Main outcome measure: Experiences, barriers, and facilitators of pharmacists and patients.

Results: Most patients (78%) would recommend the ADAPT intervention to others, and thought that the pharmacy was the right place for mHealth aiming to support adherence (63%). The possibility to monitor asthma symptoms was highly appreciated by patients and pharmacists. Pharmacists were satisfied with the ADAPT intervention (96%), and using the intervention was not time consuming (91%). The ADAPT intervention promoted contact with patients (74%) and facilitated the healthcare providing role of pharmacists (83%). Pharmacists who did not have access to the ADAPT intervention mentioned time constraints and funding as main barriers for using mHealth.

Conclusion: Pharmacists and patients perceived many beneficial effects and were positive about the ADAPT intervention. This study emphasizes opportunities for mHealth in improving the quality of care, which supports the need for further implementation in clinical practice.

INTRODUCTION

Suboptimal adherence is a major problem among patients with chronic conditions, negatively affecting health outcomes and treatment costs. On average, 50% of patients fail to adhere to the recommendations of their healthcare provider.[1,2] Information and communication technologies (ICT) are increasingly used to support patients with chronic conditions,[3-5] in particular the use of mobile health (mHealth) have increased. Mobile device technologies, such as smartphone applications (apps), may facilitate healthcare services. The development of mHealth interventions (i.e. mobile devices to support medical and public health) is rapidly increasing, because it has the potential to be efficient, is accessible, safe, cost-effective, and adjustable to one's preferences.[4,6,7] Moreover, 70% of the total population in Western Europe owns a smartphone,[8] indicating that mHealth can target many patients with chronic conditions.

MHealth interventions seem to be in particular promising for specific patient groups such as adolescents, as adherence rates decrease during adolescence and almost all adolescents (95%) own a smartphone.[9,10] During adolescence, patients start to develop their own medication beliefs and medication intake habits,[11] which may persist into adulthood. It is therefore an important life phase for interventions aiming at medication use. However, most mHealth interventions are not intended for adolescents or targeted just one aspect of disease management, e.g. a reminder to prevent forgetting,[5,12-15] while previous studies showed that solely one element does not give sufficient support to children and adolescents.[16] We developed, in co-creation with adolescents with asthma,[17] an interactive mHealth intervention with different components to support self-management; the ADolescent Adherence Patient Tool (ADAPT).[18] The ADAPT intervention supported self-management, i.e. increased medication adherence of adolescents with asthma having poor adherence rates.[19]

Further implementation and integration of mHealth in clinical practice is a complex process. Besides mHealth characteristics, the context plays an important role (such as the setting in which mHealth is used, the process of using mHealth, and the characteristics of the users).[20] Process evaluations and user experiences are therefore needed to increase the understanding of the implementation and integration of mHealth in clinical practice.[21]

Aim of the study

The aim of this study was to explore experiences, barriers, and facilitators of pharmacists and patients towards the ADAPT intervention, and to explore the perceptions of pharmacists towards mHealth interventions in general.

Ethics approval

The current study is part of the ADAPT trial, which is approved by the Medical Review Ethics Committee of the University Medical Centre Utrecht (NL50997.041.14) and by the Institutional

Review Board of Utrecht Pharmacy Practice network for Education and Research (UPPER), Department of Pharmaceutical Sciences, Utrecht University.[22] The trial is registered at the Dutch Trial Register (NTR5061). Before start of the study, all patients signed informed consent and for patients younger than 16 years, both parents also had to sign.[18,19]

METHOD

Study setting and participants

All pharmacists and patients participated in the ADAPT study; a 6-months cluster randomised controlled trial to test the effectiveness of the ADAPT intervention. The complete rationale, design, and effectiveness of the ADAPT study are described elsewhere.[18,19]

Patients (N=87) who used the ADAPT intervention were invited to complete an online questionnaire to evaluate the ADAPT intervention. Community pharmacists who had access to the ADAPT intervention (N=24) were interviewed with a structured questionnaire in order to obtain extensive information about the ADAPT intervention. In addition, pharmacists who did not have access to the ADAPT intervention (N=26) were asked to complete an online questionnaire on their perceptions towards mHealth in the pharmacy. Data was collected between May 2016 and July 2017.

ADAPT intervention

The ADAPT intervention was developed together with adolescents with asthma, and was based on the Common Sense Model of Self-Regulation.[23] The intervention consisted of an app for patients, which was connected to a desktop management system in the pharmacy. The ADAPT intervention was interactive and contained motivational, educational, and behavioural components (***Table 1***) to support self-management and adherence.[18] Patients were asked to complete the questionnaire to monitor symptoms at least once a week. Pharmacists received e-mail notifications when a patient possibly required care, and they were asked to support the patient (when needed) by using the pharmacist chat.

Questionnaire for patients who had access to the intervention

The online questionnaire for patients was designed to evaluate patient's experiences with the ADAPT intervention. The questionnaire contained open-ended and five-point Likert scale questions (totally disagree to totally agree) on the use (ease and frequency), experiences with the different components (usefulness and enjoyability), and facilitators and barriers for using the intervention in everyday life.[24] Age, gender, self-reported medication use, adherence, and symptom control of patients was registered. Personal data was encrypted using a study code, ensuring privacy of all participants.

Questionnaire for pharmacists who had access to the intervention

Pharmacists were interviewed with a structured questionnaire by a research assistant, because the aim was to obtain extensive information on the ADAPT intervention. The structured questionnaire contained questions on pharmacy characteristics and on experiences with the ADAPT intervention, i.e. about the use (ease and frequency), the experience with the different components, barriers and facilitators for use, and the perceptions on implementation and integration of the ADAPT intervention in clinical practice.[24] Additionally, pharmacists were asked to complete a short questionnaire using a five-point Likert scale (totally disagree to totally agree).

Table 1. Components of the ADolescent Adherence Patient Tool (ADAPT), an interactive mHealth intervention consisting of a smartphone application (app) for patients connected to a desktop management system for pharmacists.

Intervention component	Aim	Explanation
Weekly CARAT questionnaire	To monitor symptoms (motivational and educational)	Patients received a weekly reminder to complete this 10-item questionnaire on the app, which enables them (and their pharmacist) to monitor their asthma and allergic rhinitis symptoms over time.
Medication reminder	To prevent forgetting (behavioural)	Patients could set an alarm once or twice a day, based on their medication regimen and their preferences.
Movies	To educate and motivate	Patients received weekly movies on the app, additionally pharmacists could send specific movies to the patient's app, e.g. concerning inhaler instructions.
Peer chat	To facilitate contact	Patients could chat with peers; other asthma patients who participated in the study. This is an age-specific element, based on the adolescents' preferences.
Pharmacist chat	To facilitate contact (motivational and educational)	Patients and their pharmacists could send chat messages, e.g. ask questions or provide feedback.

App, smartphone application; CARAT, Control of Allergic Rhinitis and Asthma Test; ADAPT, ADolescent Adherence Patient Tool.

Questionnaire for pharmacists who did not have access to the intervention

Pharmacists who did not have access to the ADAPT intervention completed an online questionnaire. on their perceptions towards mHealth in the pharmacy. This questionnaire contained open-ended, closed-ended, and five-point Likert scale questions (not important to extremely important) on previous experiences, perceptions on different components, feasibility of mHealth, and barriers and facilitators for using mHealth in the pharmacy. These questions were not related to the ADAPT intervention. Moreover, the pharmacists provided basic pharmacy characteristics.

Data analysis

Descriptive statistics were calculated, such as percentages and means with standard deviations (sd). Statistical analysis were performed using IBM SPSS Statistics for Windows, version 24.0.

RESULTS

Patients about the ADAPT intervention

Of all patients who had access to the ADAPT intervention (N=87), five patients reported no use of the intervention. The characteristics of the other 82 patients (users of the intervention) are shown in ***Table 2a***. Their mean age was 15.6 ± 2.0 years, 57.3% was female, and 59.8% (49/82) of these patients did not use the mHealth intervention for the complete six-months study period. Main reasons for not using the intervention (at all) were forgetfulness (50.0%; 27/54) and technical issues (18.5%; 10/54).

Table 2a. Characteristics of the patients who used the ADAPT intervention (N=82)

	Patients % (n)
Female gender	**57.3 (47)**
Age, mean (sd)	**15.6 (2.0)**
Asthma medication use >6 years	**61.0 (50)**
Adherent (MARS ≥23)	**34.5 (30)**
CARAT controlled (CARAT >24)	**22.0 (18)**
Allergic rhinitis controlled (>8)	36.6 (30)
Asthma controlled (≥16)	29.3 (24)

ADAPT, ADolescent Adherence Patient Tool; CARAT, Control of Allergic Rhinitis and Asthma Test; MARS, Medication Adherence Report Scale; sd, standard deviation.

The majority of patients (63.4%; 52/82) used the intervention at least once a week. The questionnaire to monitor symptoms (52.4%; 43/82) and the medication reminder (23.2%; 19/82) were appreciated most. The number of users and their opinion per intervention component is shown in ***Figure 1***. The weekly Control of Allergic Rhinitis and Asthma Test (CARAT) to monitor symptoms was used by most patients (92.7%; 76/82), thereafter the movies (70.7%; 58/82), which were regarded as useful by most users (75.9%; 44/58). The peer chat was observed as 'fun to use' by most users (71.4%; 15/21), however it was used by 25.6% (21/82) of the patients. ***Figure 2*** shows the opinion of patients about the ADAPT intervention, suggesting that the intervention was not time consuming and easy to use.

The aim of the ADAPT intervention was to support self-management and increase adherence; 18.3% (15/82) of the patients reported to be more aware of their medication, and used their medication more regularly and more often. Problems with the mHealth intervention were experienced by 28.0% (23/82),

which were mainly ICT related problems with the medication reminder or app crashes. Most patients (78.0%; 64/82) would recommend the ADAPT intervention to others, with 'convenient' as the main reason. In total, 63.4% (52/82) of the adolescents agreed that the pharmacy is the right place for providing treatment related information.

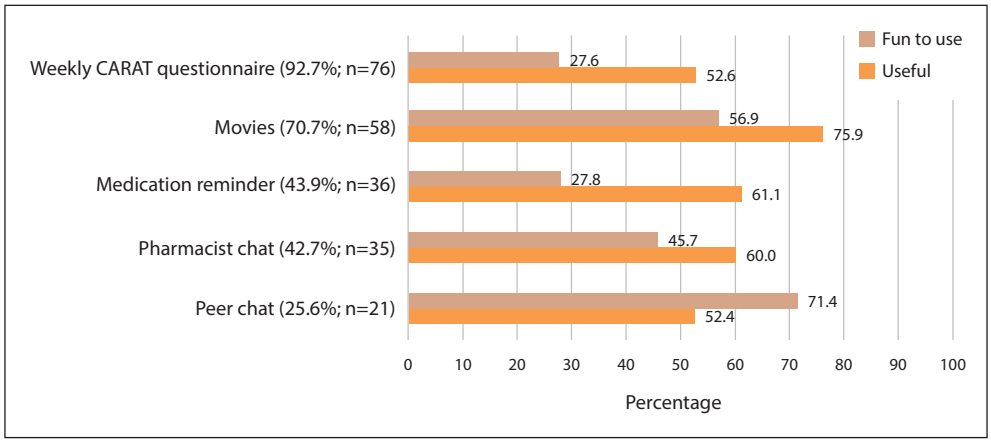

Figure 1. Self-reported use per component of the ADolescent Adherence Patient Tool (ADAPT), sorted from most to less used (N=82), and the percentage of users who perceived the component as fun to use (**brown**) or useful (**orange**).
CARAT, Control of Allergic Rhinitis and Asthma Test.

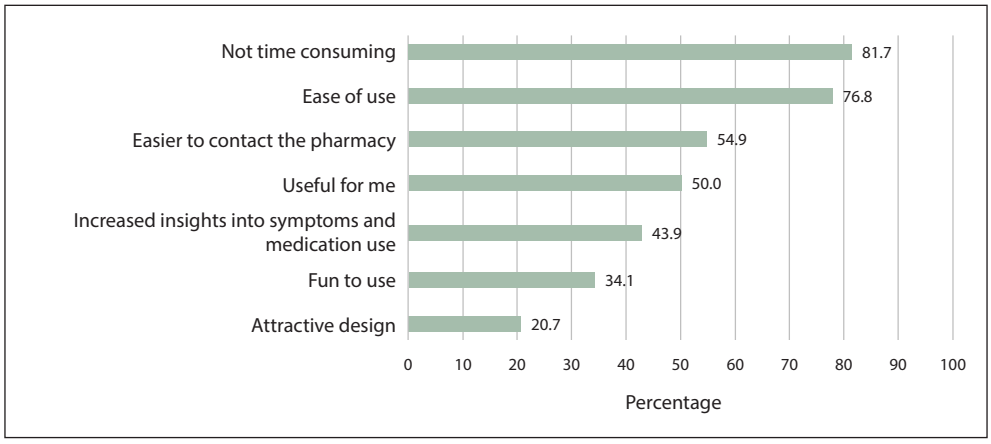

Figure 2. The percentage of patients (N=82) who agreed (totally agree and agree) with the statements about the ADolescent Adherence Patient Tool (ADAPT) intervention.

Pharmacists who had access to the ADAPT intervention

Almost all pharmacists (95.8%; 23/24) used the ADAPT intervention, reasons for not using the intervention (n=1) were not fitting with daily activities and preferably patient contact via e-mail (instead of an app). We excluded this pharmacist from further analyses. The characteristics of

pharmacists who used the ADAPT intervention (N=23) are shown in ***Table 2b***. Most pharmacists (73.9%; 17/23) used the mHealth intervention for the complete study period. Two participants were pharmacy technicians, who were specialised in pulmonary care, and in three pharmacies more than one pharmacist was responsible for the intervention.

Table 2b. Characteristics of the pharmacist study population

	Intervention group (N=23) %(n)	Control group (N=26) %(n)
Pharmacist characteristics		
Female gender	73.9 (17)	57.7 (15)
Age, mean (sd)	35.1 (9.0)	43.0 (8.8)
Working experience in years, mean (sd)	9.6 (8.1)	16.8 (8.4)
Previous experiences with mHealth	30.4 (7)	42.3 (11)
Pharmacy characteristics		
Number of pharmacists (FTE), mean (sd)	1.7 (0.6)	1.4 (0.6)
Number of pharmacy technicians (FTE), mean (sd)	6.4 (3.2)	6.1 (3.1)
Located in urban environment	65.2 (15)	65.4 (17)
Located in health centre	65.2 (15)	73.1 (19)

FTE, full time equivalent; mHealth, mobile health; sd, standard deviation.

Before the start of the ADAPT study, more than half of the pharmacists (56.5%; 13/23) were not familiar with the use of electronic health (eHealth) in the pharmacy. During the study, on average 3 ± 2 patients per pharmacy used the intervention. Using the intervention was not time consuming for most pharmacists (91.3%; 21/23; ***Figure 3***), varying from a few minutes to 20 minutes per week depending on the patient's needs. The pharmacist with most participants (n=8) spent on average five minutes per week on the intervention. Almost all pharmacists (95.7%; 22/23) were satisfied with the ADAPT intervention, and 73.9% (17/23) contacted patients, based on e-mail notifications generated by the desktop management system, such as a low asthma control score or a question via the pharmacist chat.

The use of the intervention was clear for 78.3% (18/23) and the desktop management system was regarded as user-friendly by 69.6% (16/23) of the pharmacists (***Figure 3***). The chat function with the patients and the questionnaire to monitor symptoms of the patient were appreciated most. For most pharmacists, the ADAPT intervention promoted contact with patients (73.9%; 17/23) and it supported the pharmacist's role as a healthcare provider (82.6%; 19/23). In total, 47.8% of the pharmacists (11/23) thought that the intervention improved medication use of their patients (***Figure 3***). However, the low number of patients per pharmacy, reluctance of patients, time constraints, and the non-intuitiveness of the intervention were reasons why the ADAPT intervention did not meet expectations for ten pharmacists (43.5%; 10/23). Moreover technical problems were experienced by 30.4% (7/23) pharmacists (***Figure 3***), mainly related to updates of the

desktop management system. Six pharmacists suggested an improvement in the usability of the intervention, e.g. easier login procedure. Integration of the desktop management system in the pharmacy information system would be a major improvement according to all pharmacists.

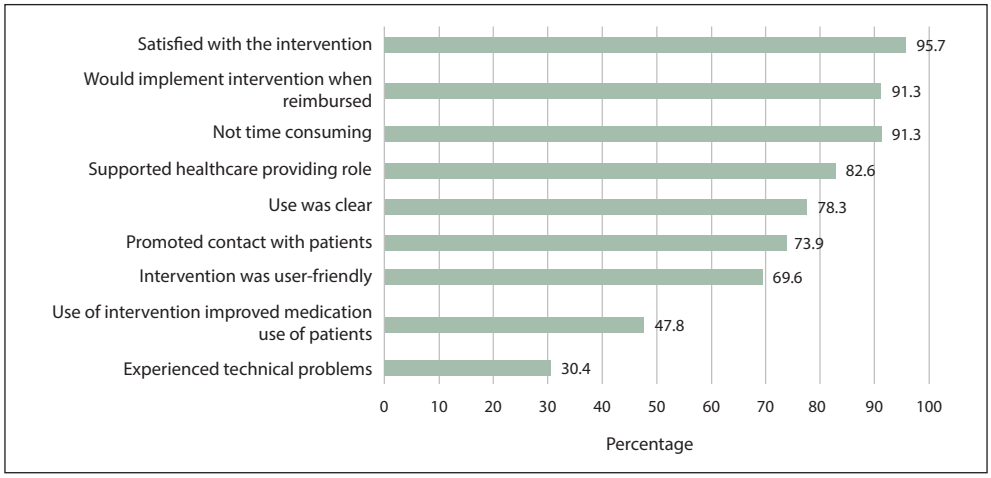

Figure 3. The percentage of pharmacists (N=23) who agreed with the statements about the ADolescent Adherence Patient Tool (ADAPT).

Most pharmacists (91.3%; 21/23) would implement the intervention when reimbursed (***Figure 3***). However, there were concerns about the patient population, as adolescents were experienced as reluctant and hard-to-reach. Pharmacists suggested older patients with chronic diseases such as diabetes, asthma/COPD, or cardiovascular diseases as a target population. The majority of pharmacists (95.7%; 22/23) agreed that the pharmacy is the right place for mHealth interventions, like the ADAPT intervention, because medication counselling and adherence were seen as the responsibility of pharmacists. Moreover, the pharmacy was suggested as easy accessible. The reason for not using mHealth in the pharmacy was that patients might prefer their general practitioner as a healthcare provider, instead of their pharmacist.

Pharmacists who did not have access to the ADAPT intervention

Characteristics of the 26 pharmacists who did not have access to the ADAPT intervention are shown in ***Table 2b***. More than half of the pharmacists (57.7%; 15/26) had never heard of mHealth interventions before. Two pharmacists used mHealth interventions previously, and almost all other pharmacists would like to use mHealth in their pharmacy (95.8%; 23/24).

Main expected facilitators for using mHealth were supporting adherence (84.6%; 22/26) and providing extra care for patients (80.8%; 21/26), while the main barriers were time constraints (53.8%; 14/26) and lack of reimbursement (46.2%; 12/26). Most pharmacists (80.8%; 21/26) thought they had sufficient skills to use mHealth, while a lack of mHealth knowledge was mentioned by

others (n=5). The majority of pharmacists (88.5%; 23/26) thought that innovations, such as mHealth, are needed to be prepared for the future.

The pharmacy was seen as the right place for mHealth interventions supporting medication use (92.3%; 24/26), because mHealth can support the healthcare providing role of pharmacists (87.5%; 21/24), medication counselling is seen as the responsibility of pharmacists (83.3%; 20/24), and the pharmacy might be more accessible than the general practitioner (66.7%; 16/24). Moreover, almost all pharmacists thought that mHealth could be useful for other chronic diseases, such as diabetes (96.2%; 25/26) and cardiovascular diseases (92.3%; 24/26). Half of the pharmacists (50.0%; 13/26) thought that mHealth is also useful for non-chronic diseases to provide extra information and to ensure correct medication use, for example with antibiotics.

Funding was seen as an important factor for implementing mHealth in daily practice, because mHealth improves medication counselling (88.5%; 23/26), using mHealth costs time (73.1%; 19/26), and (electronic) consults should be reimbursed (50.0%; 13/26). All pharmacists (N=26) would implement mHealth when reimbursed.

DISCUSSION

Pharmacists and patients were generally positive about the ADAPT intervention. Almost all pharmacists were satisfied with the intervention and the majority of patients would recommend it to others. Providing extra care for patients was one of the main reasons for using mHealth by both pharmacist groups. Pharmacists who delivered the ADAPT intervention valued the improved patient contact. Negative experiences with the ADAPT intervention were mainly related to technical problems, due to updates, which might hamper further implementation of mHealth. However, updates are important to ensure the safety and privacy of patients. Technical issues should therefore receive high priority when further implementing mHealth. Another important facilitator for further implementation is the integration of mHealth in the pharmacy information system, because a 'stand-alone' desktop program restrained the integration with the pharmacist's workflow. Although, the majority of pharmacists experienced the desktop management system as user-friendly and clear, which are important factors for acceptance and uptake.[25]

The weekly questionnaire to monitor symptoms was the most frequently used mHealth component, and it was highly appreciated by patients and pharmacists. We used the CARAT questionnaire,[26] which is a validated questionnaire consisting of ten questions on allergic rhinitis and asthma symptoms. Monitoring symptoms contributes to improved health outcomes[27] and based on the current positive perceptions, we recommend a short questionnaire as a useful component for mHealth interventions. Pharmacist also highly appreciated the possibility to chat with patients, while they experienced some non-response of patients. Chatting with patients, i.e. an electronic consultation (e-consult), provide patients with the opportunity to ask questions, while pharmacists can answer them when it fit with their daily activities.

A unique aspect for patients is that they can re-read the consult when needed.[28] E-consults are new for patients and pharmacists, therefore more research should be conducted towards effective ways of digital communication with patients.

For both patients and pharmacists, the use of the ADAPT intervention was not time consuming, however time constraints were named as an important barrier for using mHealth by pharmacists who did not have access to the ADAPT intervention. For further implementation it is therefore important to emphasize that the ADAPT intervention was not time consuming for 91% of the pharmacists. Moreover, integration of the desktop management system in the pharmacy information system will support efficient use of the intervention. Regardless of the efficient use, the ADAPT intervention might become more time consuming, when implemented among all adolescents with asthma. Because on average 18 adolescents per pharmacy use asthma medication,[19] while in the ADAPT study on average three patients per pharmacy participated. Nonetheless, the time spend on the ADAPT intervention depended on the patient's needs and the intervention should not be seen as something extra, instead it can replace other tasks, such as consultations and medication reviews, and thereby save time on the long-term.

In the current study, the pharmacy was seen as the right place for mHealth interventions like, the ADAPT intervention. In the Netherlands, every patient is registered at one pharmacy and mostly fill all their prescriptions there. As a medication expert and healthcare provider, pharmacists are responsible for medication counselling and adherence. They can thereby improve the quality of patient care and outcomes. MHealth interventions can facilitate the pharmacist's responsibilities and promote contact with patients. This is important nowadays, because pharmacists are expected to combine their management role with a more healthcare providing role, and there is an ongoing shift towards integrated care settings.[29] Currently, not many mHealth interventions are designed in pharmacies,[4,6,30] while positive effects of pharmacy delivered mHealth interventions are shown for disease management of several chronic diseases in adult patients.[31,32] In the current study, even non-chronic medication users were mentioned as a target group for mHealth. Therefore further research should focus on the implementation and integration of mHealth in pharmacy practice.[31]

Intuitive usability and clear explanations of mHealth intervention were suggested to support the usability and are therefore important for further implementation. A previous study also showed the importance of training for using mHealth interventions.[25] However, firstly, pharmacists should be aware of the possibilities for mHealth in the pharmacy, because in the current study only a minority of pharmacists was familiar with mHealth and/or eHealth. Moreover, pharmacy students would like to recommend mHealth to their future patients,[33] i.e. there is room for improvement.

All pharmacists and patients voluntary participated in the ADAPT study and might therefore be more enthusiastic and positive about mHealth, or more motivated to use the ADAPT intervention. Thus, the current study might contain a response bias. Nonetheless, this evaluation study gives insights into the perceptions of patients and pharmacists about a mHealth intervention, and it highlighted main barriers

and facilitators for using mHealth in a pharmacy setting. This is important for (research towards) further implementation and integration of mHealth in clinical practice. Our exploratory findings should be taken into account when developing mHealth interventions to support self-management and adherence. However, more research is needed towards the evaluation of mHealth interventions in the pharmacy to generalize our findings and towards the cost-effectiveness of mHealth, which is important for the development of reimbursement guidelines.

CONCLUSION

Both patients and pharmacists perceived beneficial effects and were positive about the ADAPT intervention. The intervention was not time consuming, while time constraints were an expected barrier by pharmacists who did not deliver the ADAPT intervention. Moreover, the ADAPT intervention facilitated the pharmacist's role as a healthcare provider and promoted contact with patients. Attention should be paid to prevent technical issues and to ensure reimbursement guidelines. The pharmacy setting was seen as a right place for mHealth interventions supporting appropriate medication use, also for patients other than asthma patients. This study emphasized the opportunities for mHealth in improving the quality of care. The current findings should be emphasized among pharmacists, other healthcare providers, and intervention developers. Further research should focus on generalizability of our findings and on the further implementation and integration of mHealth in the (pharmacy) healthcare setting.

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CHAPTER 5.2

Potential normalization of an asthma mHealth intervention in community pharmacies: applying a theory-based framework

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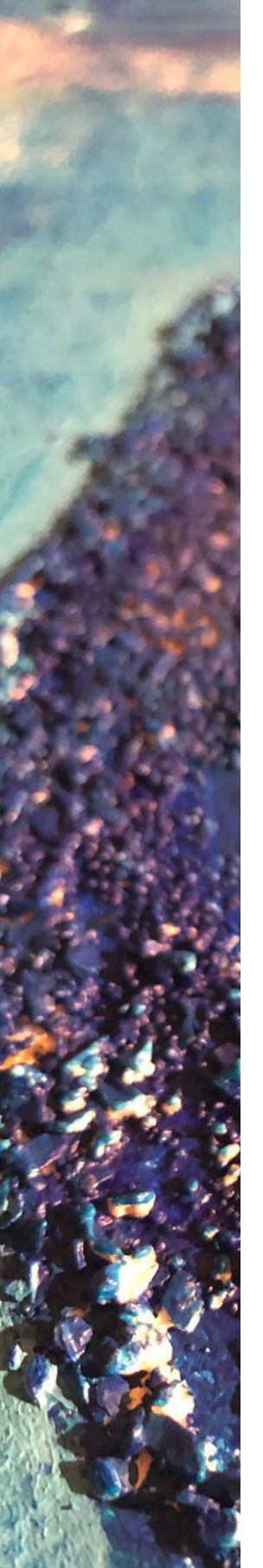

ABSTRACT

Background: Effective mobile health (mHealth) interventions have been developed to support patients with their medication use, however few are widely used in clinical practice. Normalization of an intervention is essential to have a population impact, which is defined as the process of getting a new intervention into routine practice.

Objective: The aim of this study was to assess the normalization potential of a complex mHealth intervention for adolescents with asthma (ADolescent Adherence Patient Tool; ADAPT) in daily community pharmacy practice.

Methods: We applied the Normalization Process Theory (NPT), a sociological action theory, to study the normalization potential of ADAPT. NPT explains factors that promote or hinder implementation, embedding, and integration of new interventions in clinical practice. We used evaluation data (questionnaires) of 23 pharmacists who used the ADAPT intervention. These data were collected as part of the process evaluation of the ADAPT study.

Results: Pharmacists understood the purpose of ADAPT and were prepared to undertake the necessary work of implementation; however, the time required to implement the intervention was a significant barrier in the absence of appropriate reimbursement mechanisms. The potential for normalization could be enhanced by the use of product champions and appropriate reimbursement, to ensure the participation of pharmacists. Support from professional bodies for the use of mHealth would also promote normalization.

Conclusions: Normalization of mHealth is a complex continuous process. The ADAPT intervention has the potential to be normalized in the community pharmacy, but full normalization would require changes in pharmacy practice and reimbursement models.

INTRODUCTION

Suboptimal asthma control is common, mostly caused by medication non-adherence. These non-adherence rates are especially high during adolescence.[1] Mobile health (mHealth) interventions have the potential to support patients with their medication use.[2,3] Several mHealth interventions have been developed and resulted in increased adherence rates, improved self-management, or improved health status.[4-7] However, there is a delay in the implementation of such mHealth interventions in daily healthcare practice, also known as the 'research to practice gap'.

MHealth interventions are often complex, i.e. containing multiple interconnecting components, because these have been shown to be more effective than interventions aimed at only one aspect of non-adherent behaviour.[8,9] Complex interventions may be hard to implement in clinical practice, as they often require change at multiple levels involving different stakeholders, e.g. the patient, the healthcare professional, the healthcare organisation, and the wider environment such as the national healthcare system.[10-14] These contextual factors are dynamic and can change over time. It has been suggested that the fit between an intervention and its context determines the success of the implementation.[10]

The Normalization Process Theory (NPT), a sociological theory, focusses on the work required to implement new interventions in clinical practice. Normalization is defined as *"to become part of routine practice"*, and it covers different stages: implementation, embedding, and integration (***Table 1***).[15,16] NPT was developed to address factors that promote and hinder implementation, embedding, and integration of new practices.[15] It can be used to describe how complex healthcare interventions can become normalized.

Table 1. Terminology and definitions used in the Normalization Process Theory (NPT)

Term	Definition
Normalization	To become part of routine practice, i.e. to take it for granted
Embedding	The process through which a practice (e.g. use of a new intervention) becomes routinely incorporated in everyday work of individuals and groups
Implementation	The social organisation of bringing a practice (e.g. use of a new intervention) into action, thus actually using the intervention
Integration	The process by which a practice (e.g. use of a new intervention) is reproduced and sustained among social matrices of an organisation or institution

We showed that the ADolescent Adherence Patient Tool (ADAPT), a pharmacy based interactive mHealth intervention, improved adherence in adolescents with asthma having poor adherence rates.[17] However, the population impact of an intervention is dependent on both the effect size and the extent to which the intervention reaches the target population.[18] Thus the impact of an intervention is likely to be enhanced by integration into routine clinical practice.[11,16] Most previously developed mHealth interventions were local or isolated initiatives, and not much attention has been paid to a sustained normalization plan.[6,7,19] Therefore, we aimed to study the normalization potential of a mHealth intervention for adolescents with asthma in the community pharmacy, using the ADolescent Adherence Patient Tool (ADAPT) as an example.

METHODS

Study design, setting, and participants

We applied the NPT retrospectively, per construct and per component, to the ADAPT intervention.[17,20] The NPT Toolkit, consisting of 16 questions,[21] was used to evaluate the implementation, embedding, and integration of ADAPT in daily pharmacy practice. Evaluation data from the ADAPT study were used when applying NPT (***Chapter 5.1***). The ADAPT study was cluster randomised controlled trial to evaluate the ADAPT intervention in Dutch community pharmacies. At the end of the ADAPT study, a research assistant administered a structured interview to 23 pharmacists who used the intervention. This structured interview (i.e. questionnaire) contained open-ended questions on their experiences with the ADAPT intervention and their perceptions on implementation and integration in clinical practice. The pharmacists also completed a brief questionnaire where they used a five-point Likert scale (totally agree to totally disagree) for statements related to their experiences and opinions about the ADAPT intervention.[17,20]

Normalization Process Theory (NPT)

NPT is a sociological action theory, proposing first that complex interventions become routinely embedded and integrated in contexts as the result of people working, individually and collectively, to implement them. Action is regarded as more important than people's attitudes or intentions, when implementing an intervention in healthcare. Second, the work of implementation is operationalized through four constructs of social action (***Table 2***); (1) *coherence:* does it makes sense?, (2) *cognitive participation:* do I want to take part?, (3) *collective action*: what is the impact on work?, and (4) *reflexive monitoring*: is it worth it? These constructs represent different stages and different kinds of work that people do as they work around a set of new practices, such as the use of a new intervention. Lastly, NPT proposes that the integration of a complex intervention requires continuous investment by people that carry forward in space and time. Meaning that continuous investing in sense-making, effort, commitment, and appraisal are necessary for the normalization of a complex intervention.

Table 2. The four constructs of the Normalization Process Theory (NPT) with the four corresponding components

Construct	Component	Explanation
Coherence *Sense-making*	Internalization	Understanding the value, benefits, and importance
	Individual specification	Understanding specific individual tasks and responsibilities
	Differentiation	Understanding the distinctiveness
	Communal specification	Working together with others to build a shared understanding of the aim, objective, and expected benefits
Cognitive participation *Effort*	Initiation	Key participants drive implementation forward
	Enrolment	Organising or reorganising of participants (and others) to collectively contribute
	Legitimation	Ensuring that other participants believe it is right for them to be involved, and can make a valid contribution
	Activation	Defining the actions and procedures needed to sustain using mHealth and stay involved
Collective action *Commitment*	Interactional workability	Impact on interactions, particularly the interactions between healthcare professionals and patients (consultations)
	Relational integration	Impact on relations between groups of professionals
	Skill set workability	Fit between new intervention and existing skill set
	Contextual integration	Fit with overall organisational context; goals, morale, leadership and resources
Reflexive monitoring *Appraisal*	Systematization	Determining how effective and useful it is for participants and for others
	Communal appraisal	Working together (in formal collaboratives or in informal groups) to evaluate the worth
	Individual appraisal	Working experientially as individuals to appraise its effects on them and the contexts in which they are set
	Reconfiguration	Attempting to redefine procedures or modify the intervention itself

ADolescent Adherence Patient Tool (ADAPT)

The ADAPT intervention consisted of a smartphone application (app) for patients, which was connected to a desktop management system of the patient's community pharmacist. In the Netherlands, patients usually collect all their prescriptions in a single pharmacy. The ADAPT intervention was an interactive mHealth intervention with several components to support different aspects of medication adherence and self-management: a weekly questionnaire to monitor symptoms, a medication reminder, short educational and motivational movies, a peer chat, and the opportunity to contact the pharmacist. Details have been described elsewhere.[17,20]

Pharmacists were asked to support patients with their medication use by contacting them via chat messages, sending additional movies, and adjusting the frequency of the questionnaire to monitor symptoms (if needed). Pharmacists received e-mail notifications when patients sent a chat message and when the weekly symptom questionnaire indicated poor symptom control. The ADAPT intervention was evaluated in a six months cluster randomised controlled trial with 234 patients, and improved adherence in adolescents with asthma having poor adherence rates.[17]

Data analysis

The structured interviews were audiotaped and the recordings were transcribed verbatim. Summaries of responses to each question were made, and a combination of analytical techniques (searching and finding) and tactics (connecting) were used to obtain a comprehensive data overview. Data were then mapped onto NPT. Questionnaire data were divided in three groups per statement: agree (fully agree and agree), neutral, and disagree (disagree and totally disagree). Descriptive statistics were calculated using IBM SPSS Statistics for Windows (version 24.0).

RESULTS

The characteristics of participating pharmacists are shown in ***Table 3***, and the results of the brief questionnaire are shown in ***Table 4***. The results of the application of NPT to ADAPT are described below and summarized in ***Figure 1***.

Table 3. Characteristics of the study population (N=23)

	Mean (sd)
Pharmacist characteristics	
Female gender, %(n)	73.9 (17)
Age (years)	35.1 (9.0)
Working experience (years)	9.6 (8.1)
Number of patients who participated per pharmacy	3.3 (1.8)
Pharmacy characteristics	
Pharmacists (FTE)	1.7 (0.6)
Pharmacy technicians (FTE)	6.4 (3.2)
Located in urban environment, %(n)	65.2 (15)
Located in health centre, %(n)	65.2 (15)

FTE, full time equivalent; sd, standard deviation.

Coherence

The concept of coherence refers to the extent to which users can make sense of the intervention. There are four subsidiary constructs: differentiation (the extent to which the intervention can be differentiated from similar interventions), communal specification (shared understanding of

intended benefits), individual specification (individual understanding of the intended benefits and the work required to realise these benefits), and internalization (understanding the value, benefits, and importance of the intervention).[21]

Differentiation

Pharmacists in this study were easily able to differentiate ADAPT from alternative methods to improve adherence to asthma medication, as for most of them, this was their first experience with mHealth in the pharmacy. The ADAPT intervention consisted of a unique combination of interactive components to improve adherence. Pharmacists were aware that the desktop management system enabled the use of multiple components, such as the pharmacist chat, that facilitated contact between patients and pharmacist (***Table 4***). These electronic consults (e-consults) were new for patients and pharmacists.

Table 4. Overview of the pharmacists' opinion (N=23) about the ADolescent Adherence Patient Tool (ADAPT)

	Agree % (n)	Neutral % (n)	Disagree % (n)
Before start of the study			
I am familiar with electronic health in the pharmacy	30.4 (7)	13.0 (3)	56.5 (13)
The training was useful[a]	66.7 (12)	33.3 (6)	*N/A*
Use of the ADAPT intervention			
I used the intervention during the whole study period	73.9 (17)	*N/A*	26.1 (6)
Use of intervention was clear	78.3 (18)	8.7 (2)	13.0 (3)
Use of intervention was not time consuming	91.3 (21)	4.3 (1)	4.3 (1)
Evaluation of the intervention			
I'm satisfied with the intervention	95.6 (22)	*N/A*	4.4 (1)
Use of the intervention resulted in better insight in symptoms and medication use of patients	56.5 (13)	30.4 (7)	13.0 (3)
Use of the intervention resulted in improved medication use of patients	47.8 (11)	34.8 (8)	17.4 (4)
Use of the intervention facilitated contact between patients and pharmacists	73.9 (17)	21.7 (5)	4.3 (1)
Use of the intervention assisted the pharmacist with medication guidance of patients	82.6 (19)	13.0 (3)	4.3 (1)
Further implementation			
I require additional information to implement the intervention in clinical practice	30.4 (7)	26.1 (6)	43.5 (10)
Integration of the ADAPT desktop application in the pharmacy computer system will support implementation	100 (23)	*N/A*	*N/A*
I would like to use the intervention when reimbursed	91.3 (21)	*N/A*	8.7 (2)
The pharmacy is the right place for mHealth	95.6 (22)	*N/A*	4.3 (1)

[a] In total, 18 pharmacists participated in the training.

ADAPT, ADolescent Adherence Patient Tool

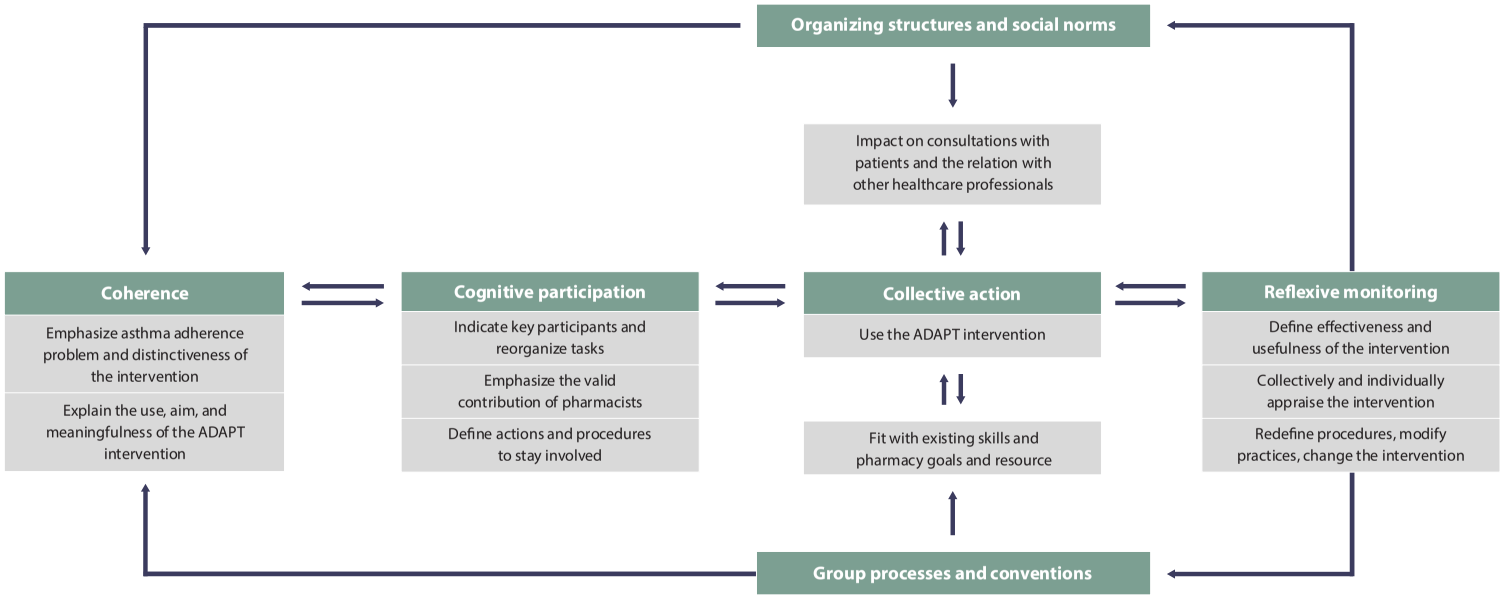

Figure 1. The Normalization Process Theory (NPT) model applied to the ADolescent Adherence Patient Tool (ADAPT); an interactive asthma mobile health (mHealth) intervention in the pharmacy setting.

Communal specification

Pharmacists were aware of the problem of sub-optimal adherence to asthma medication in adolescents, agreed that this was an important problem, and understood that ADAPT aimed to improve adherence. Moreover, almost all pharmacists (22/23) thought that the pharmacy is the right place for mHealth interventions, like ADAPT, mainly because the pharmacy is easy accessible and medication counselling is the responsibility of pharmacists.

"The pharmacy is the right place for mHealth interventions like ADAPT, because medication adherence and medication counselling belong to pharmacists."
Male pharmacist, age 50 years

Individual specification

To ensure individual specification, we organised a half-day training, at the start of the ADAPT study, which was rated as useful by two thirds of the pharmacists who attended the training (***Table 4***). In addition, pharmacists received an explanation in the pharmacy and we designed an intervention guide to explain the (use of the) intervention. Most pharmacists (18/23) stated that they understood their specific tasks and responsibilities, such as using the intervention when receiving e-mail notifications but some reported (7/23) requiring additional information to help implement the intervention in clinical practice, and suggested an electronic support manual integrated into the intervention.

"*The e-mail notifications were easy to deal with and they could easily be found in the system."*
Female pharmacist, age 29 years

Internalization

The aim of the ADAPT intervention was to increase adherence, because adherence among adolescents with asthma is low, resulting in uncontrolled disease.[20] As participation in the ADAPT research was voluntary, those pharmacists were self-selecting and not surprisingly, already convinced of the importance of improving adherence. However, at the start of the ADAPT study, only 7 out of 23 pharmacists were familiar with the use of electronic health (eHealth) interventions in the pharmacy, including mHealth. Thus future implementation strategies should include an emphasis on the importance of adherence and the benefits of the ADAPT intervention as a starting point to ensure sense-making among pharmacists as well as providing information about the potential benefits of mHealth.

Cognitive participation

The second stage of normalization is about commitment, i.e. '*do I want to participate*', including the role of key participants, reorganisation of tasks, and defining actions to stay involved. The four constructs which make up cognitive participation are initiation, enrolment, legitimation, and activation.[21]

Initiation

Initiation refers to the extent to which key participants drive the work of implementation forward. In this case, pharmacists were expected to support patients by chat messages, sending additional movies, and adjusting the frequency of the symptom questionnaire if needed. In this study, initiation was supported by the research team sending a monthly digital newsletter aiming to motivate and remind the participating pharmacists to be actively involved in the intervention. Data showed that most pharmacists did contact the patients through the pharmacist chat, and monitored the symptoms of the patients. However, not many additional movies were sent.

Enrolment

Enrolment refers to the extent to which participants have to (re-)organise themselves and others in order to implement the intervention. Pharmacists need to change their daily routine in order to create time to use a new intervention. As the number of enrolled adolescents per pharmacy was relatively low, the total time devoted to the use of the ADAPT intervention remained limited (***Table 4***). This supported enrolment in the context of this research study, but it was clear that if use of this intervention were to become more widespread, the time required would be a significant barrier unless reimbursement systems were changed to reflect this additional work. Twenty-one of the 23 participating pharmacists stated they would only continue to use the ADAPT intervention in clinical practice if their time was reimbursed.

"Use of the ADAPT intervention cost very little time, approximately 5-10 minutes per week"
Male pharmacist, age 40 years

Legitimation

Legitimation refers to participants believing that promoting the implementation is a legitimate part of their role. Almost all pharmacists in this study thought that the pharmacy was the right place for mHealth interventions like ADAPT (***Table 4***). Moreover, around half of the pharmacists thought that they could make a valid contribution, because the ADAPT intervention resulted in improved medication use (11/23) and the intervention improved their insights into patients' asthma symptoms and medication use (13/23).

Activation

Activation is about defining actions and procedures to sustain involved with the intervention. In order to support pharmacists, we developed an intervention guide to explain the (use of the) intervention. Moreover, in the desktop application we added a decision tree to support proper use of the intervention, i.e. define the appropriate actions. Additionally, pharmacists received e-mail notifications when patients needed help and a monthly digital newsletter reminded pharmacists to stay involved. For most pharmacists, the use of the intervention was clear and they used the intervention for the whole study period (***Table 4***).

"The ADAPT intervention was handy to work with, it was very clear to me."
Female pharmacist, age 29 years

Collective action

The next stage of the normalization process is collective action, which refers to the impact on work and workflows of getting the intervention routinely embedded in clinical practice. The four constructs of collective action are interactive workability, relational integration, skill set workability and contextual integration. In the ADAPT study, most pharmacists (17/23) used the ADAPT intervention during the whole study period.

Interactional workability

Interactional workability refers to the extent the intervention improved interactions between pharmacists and adolescents. In total, 17 of the 23 pharmacists agreed that the intervention facilitated such contact. In particular the e-consults were an addition to current consultations and they contributed to co-operative interactions, such as shared-decision making.[22]

"I used the chat quite often. The patient completed the questionnaire to monitor symptoms which was nice, and sometimes I needed to contact the patient based on the symptom score. The immediate contact through the chat was new, because normally I would call them afterwards."
Male pharmacist, age 31 years

Relational integration

Relational integration refers to the impact of the intervention on accountability, responsibility, and trust between the users. The ADAPT intervention supports the healthcare providing role of pharmacists, as for most pharmacists (19/23) the intervention assisted the medication guidance of patients.

Skill set workability

Skill set workability is the extent to which existing skills of professionals fit with a new intervention. The use of the ADAPT intervention was allocated to pharmacists, as their responsibility is to ensure right medication use of patients. In two pharmacies, a pharmacy technician was appointed to use the ADAPT intervention. Moreover, the use of mHealth in clinical practice is new, it is therefore important that pharmacists are assisted with the right skills to support normalization, these skills can be acquired through trainings and workshops.[23] For most pharmacists the use of the ADAPT intervention was clear and most pharmacists thought the training was useful (***Table 4***).

"Clear instructions. I liked ADAPT."
Female pharmacist, age 25 years

Contextual integration

Contextual integration refers to the fit with the overall organisational context. The ADAPT intervention contributed to integrated care and it delivered tools to pharmacists for medication counselling and for providing extra care, which does fit with the ongoing expanding role of pharmacists.[24] All pharmacists thought that an integration of the ADAPT stand-alone desktop application in the pharmacy computer system would support further implementation (***Table 4***).

Reflexive monitoring

The last stage of normalization is reflexive monitoring, which is the appraisal work that people do, covering the effectiveness of the intervention and the redefinition of procedures. The four constructs which contribute to reflexive monitoring are systematization, communal appraisal, individual appraisal and reconfiguration.

Systematization

Systematization refers to the evidence for the effectiveness and usefulness of an intervention. The ADAPT intervention was evaluated in a cluster randomised controlled trial, showing that the intervention effectively improved adherence in adolescents with poor adherence rates.[17] The pharmacist chat was the most effective component, which was in line with previous studies.[25]

Communal and individual appraisal

Communal and individual appraisal refers to working together, or individually, to evaluate the worth of the intervention and to appraise its effects on them and on the contexts. Almost all pharmacists (95.6%) were satisfied with the ADAPT intervention. They were in general positive about the effect of the intervention for patients and themselves (***Table 4***).

"I really liked participating in the ADAPT study and the training at the start was also very nice."

Female pharmacist, age 29 years

Reconfiguration

Reconfiguration is about attempts to redefine procedures, modify practices, and changing the intervention itself. The ADAPT intervention was especially effective in improving adherence in patients with poor baseline adherence rates.[17] It might therefore be useful if pharmacists could select non-adherent patients and provide them access to the intervention, i.e. tailor the intervention. Additionally, an integration of the ADAPT intervention in the pharmacy computer system and reimbursement guidelines will support the normalization of the intervention (***Table 4***).

DISCUSSION

This study describes all factors related to the normalization of a complex asthma mHealth intervention in the community pharmacy setting. The findings suggest that the ADAPT intervention has the potential to become normalized in clinical practice as long as there is adequate financial reimbursement for the additional work required by pharmacists, and there is sufficient investment in training and motivating pharmacists to use it. These factors require change at the health service level, and lack of such change may inhibit the normalization of mHealth in clinical practice.

The context of an intervention is important when trying to implement it in clinical practice.[10,16] In the current study, a mHealth intervention for adolescents with asthma in the community pharmacy was used as an example. Thus, the normalization potential may differ for other contexts or patient populations. Moreover, it should be taken into account that trials, like the ADAPT study, are not best suited to evaluate the normalization potential of complex interventions. Trials are closed systems with strict requirements for the population and intervention use, while interventions should eventually be integrated in a dynamic real-world environment. Therefore, ideally the intervention should be continuously evaluated during an implementation phase, after the efficacy of the intervention has been shown.[26]

If the ADAPT mHealth intervention is normalized, it has the potential to facilitate integration of care among different healthcare providers (including pharmacists, physicians, and nurses). For example the physician's role might be affected if the healthcare providing role of pharmacists increases.[27] Further research should therefore focus on the inclusion of other healthcare practices. Ultimately mHealth might be added to multidisciplinary treatment guidelines to support normalization.

Different research fields focussed on the implementation of new interventions in healthcare,[10-14] and many models have been developed.[13,28,29] For example cognitive science suggests that increased knowledge increases implementation, behavioural science suggests that implementation is influenced by feedback and incentives, marketing science suggests a clear and attractive intervention, social science suggests a change in social norms, and organisational science suggests a change on system levels.[12] We chose to use a sociological model, because sociology (i.e. the study of human social relationships, institutions, and society) is important when focussing on the implementation of new interventions in a complex and dynamic everyday healthcare setting.[30] Moreover, it is time to start implementing mHealth,[31] and NPT is an action theory, proposing that the implementation of an intervention in healthcare is the product of action, not necessarily people's attitudes or intentions. NPT also highlights all relevant aspects related to normalization (implementation, embedding, and integration), which makes it a complementary theory.

Limitations

In the current study, we studied the normalization potential of a mHealth intervention by retrospectively applying the NPT and this has some limitations. Firstly, NPT is a conceptual model, while the first step in normalizing an intervention is to actually use the intervention. However, this study highlights aspects which are important for the normalization, and thereby might need extra attention when trying to get a new intervention in routine practice. Secondly, pharmacists of the ADAPT study voluntarily participated in the study and were probably positively biased, because they already understood the ADAPT intervention (sense-making and cognitive participation) and were therefore motivated to participate. Further research should focus on how to get other pharmacists (with a neutral or negative attitude) involved in using mHealth. The first steps to do this are described in the current study; ensure sense-making and cognitive participation. Support from the pharmacist community to support mHealth is also important to attain greater implementation.

CONCLUSIONS

Normalization of a complex mHealth intervention, like ADAPT, is a complex process, which involves changes at different levels and requires continuous investment of pharmacists. The ADAPT intervention has the potential to become normalized, as sense-making, effort, commitment, and appraisal were predominantly positive. However changes in pharmacy practice are needed to integrate mHealth into daily routine practice, such as changes in the intervention, work flow, and appointing a key person. Moreover, reimbursement is essential to promote implementation and professional bodies should support the use of mHealth to ensure normalization.

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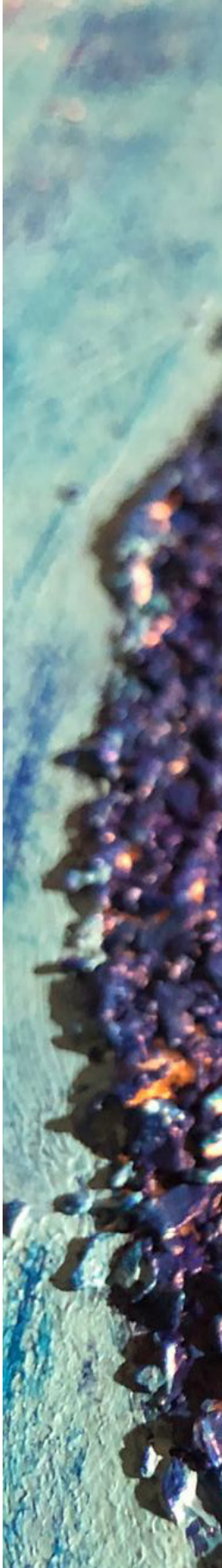

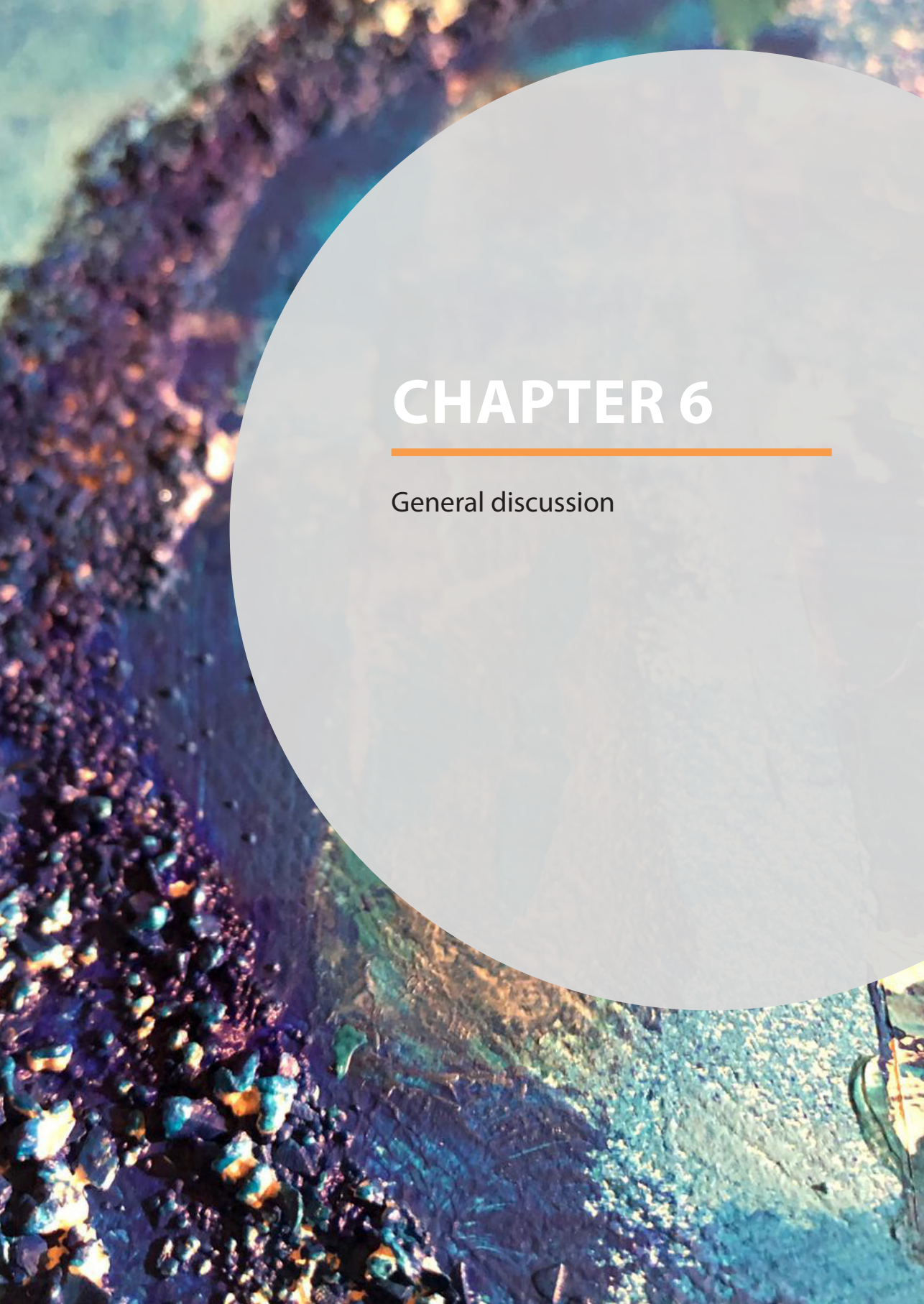

CHAPTER 6

General discussion

The overall aim of this thesis was to evaluate perspectives of adolescents on medication use and to evaluate the effect of a pharmacy-based mobile health (mHealth) intervention on adherence and self-management in adolescents.

Adolescence is a life phase where unique physical, social, and psychological changes occur. Adolescents become independent individuals and thereby more and more responsible for self-management and medication use. This developmental phase poses a challenge for the adolescent patient, his family or carers, and the healthcare provider.[1]

Adherence among adolescent patients has been reported to be relatively low compared to other age groups. Adolescent's habits, perceptions, attitudes, and beliefs towards medication, might affect medication use later in life. Adolescence is therefore an age period in which self-management including appropriate use of medication can be taught for later in life. However not much is known about adolescents' health behaviour and medication use, as most studies focus on younger children (and their parents), or study children and adolescents as one group.

Pharmacists might play an important role in stimulating good medication use of adolescents, as medication counselling is an important task for the pharmacist. Nowadays, pharmacists are increasingly expected to support appropriate use of medication in integrated care settings.[2] However, adolescents are not often seen in the pharmacy.[3]

Interactive mHealth interventions can support patients with their medication use, and have the potential to facilitate contact between patients and healthcare providers. MHealth may be particularly suitable for adolescent patients,[4] because the current generation are digital natives[1]. Surprisingly, until now, not many mHealth interventions are specifically developed for adolescent patients with chronic conditions.

MAIN FINDINGS

Chapter 2 gives an overview of medication use throughout adolescence. The most frequently used medicines by adolescents act on the nervous system, the respiratory system, and on the skin. Methylphenidate, intended for attention-deficit/hyperactivity disorder (ADHD), was the most frequently prescribed drug.

The studies in ***Chapter 3*** describe the perspectives of adolescents on their (chronic) medication use. We focused on drugs used for treatment of the most common disorders identified in ***Chapter 2***: atopic dermatitis, ADHD, and asthma. Adolescents with these conditions expressed similar low adherence rates (around 40%). They mainly tend to forget their medication. Additionally,

[1] A person who grows up in the digital age.

adolescents with atopic dermatitis developed their own way of using topical corticosteroids, which deviates from the prescribed treatment regimen (***Chapter 3.1***).

Adolescents with atopic dermatitis had incorrect beliefs about the mechanism of action and perceived limited time for daily application of creams. However, they were generally satisfied with the efficacy of their treatment, although they preferred a faster and more persistent effect (***Chapter 3.1***).

Almost all adolescents had low concerns about their medication. Adolescents with ADHD and atopic dermatitis also perceived low needs, i.e. they had an indifferent attitude toward their medication (low concerns and low necessity beliefs). Adolescents with asthma perceived somewhat more necessity toward use of their medication (***Chapter 3***).

Adverse effects of ADHD medication were mentioned as major problems; half of the adolescents experienced side effects, such as decreased appetite and sleep difficulties (***Chapter 3.2***). Adolescents with atopic dermatitis experienced mainly cosmetic side effects, such as stickiness and bad odour. Adolescents with abundant use of topical corticosteroids also reported a thinner skin as adverse effect (***Chapter 3.1***). Adolescents with asthma did not report any adverse effect, however they reported low disease control, which was associated with a lower quality of life (***Chapter 3.3***).

To target the non-adherence problem in adolescents with asthma we developed an interactive mHealth intervention; the ADolescent Adherence Patient Tool (ADAPT). This intervention was based on the needs and preferences of adolescents (explored during both quantitative and qualitative studies), and consisted of a smartphone application (app) for patients, which was connected to a desktop management system in the pharmacy. The intervention contained different functionalities: questionnaires to monitor symptoms and adherence, a medication reminder, short movies, a pharmacist chat function, and a peer chat. We evaluated the effectiveness of the ADAPT intervention in a cluster randomised controlled trial in community pharmacies. The complete rationale and design of the ADAPT study are described in ***Chapter 4.1***.

The ADAPT intervention was not effective for all adolescents with asthma that participated in the study. The intervention only increased self-reported medication adherence in adolescents with poor adherence rates at baseline and was even more effective in non-adherent patients with uncontrolled asthma (***Chapter 4.2***). We also monitored actual use of the ADAPT app (***Chapter 4.3***). Female adolescents used the app more frequently compared to male adolescents, however there was no difference in effectiveness between gender. The questionnaires to monitor asthma symptoms and adherence, and the short movies were the most frequently used functionalities. The quantity of app use did not affect adherence in the intervention group. However, adherence significantly improved in adolescents who used the chat function to contact their pharmacist, compared to those refrained to do so.

In ***Chapter 5*** we described the possibilities for further implementation of mHealth interventions in the community pharmacy. In order to explore the potential of mHealth, we performed a process evaluation (***Chapter 5.1***). Pharmacists and patients were both positive about the ADAPT intervention, and felt the intervention was not time consuming. Pharmacists also mentioned that the intervention promoted contact with their patients, and that it facilitated their role as a healthcare provider. However, getting a new intervention into routine practice (i.e. normalization) is a complex and continuous process, as discussed in ***Chapter 5.2***. Based on our results, we conclude that mHealth interventions, such as ADAPT, can potentially be normalized in community pharmacies. However it requires changes in current pharmacy practice, such as changes in the workflow, because continuous investment of pharmacists is required. The normalization potential of mHealth could further be enhanced by the use of product champions (i.e. key participants), appropriate reimbursement models, and by support of professional bodies.

In this general discussion, we will elaborate on the results described in this thesis, place them in a broader perspective, and propose recommendations for further research. Additionally, we will explore the opportunities for mHealth in healthcare and provide recommendations for effective use of mHealth in clinical practice.

STUDIES IN THE ADOLESCENT PATIENT POPULATION

Studies often classify adolescents within paediatrics, which covers a broad age group, including infants, children, and adolescents. However, ideally adolescents should have their own classification (and physician), because the studies described in this thesis show that adolescents face unique barriers and have their own beliefs, needs, and preferences when it comes to healthcare and medication use (***Chapter 3***).[5-7] Forgetting, low necessity beliefs, and a lack of treatment knowledge are becoming main barriers for not taking medication as prescribed.[8] These barriers and perspectives differ from adults and children (mostly parents manage their child's medication use), and are therefore specific for adolescents.

Another distinctive characteristic of adolescents is the effect of their social environment; embarrassment is an important example. Some adolescents with atopic dermatitis even reported to adjust their clothing to cover their affected skin (***Chapter 3.1***) and adolescents with asthma are more reluctant to use their inhalers when they have to leave the classroom, or in a lack of privacy.[9,10] Opinions of peers are important at this age, and insufficient support of teachers, nurses, coaches, or friends are barriers for medication use.[5,10] Social media may also influence the life of adolescents. For example online influencers[2] can affect their behaviour. Here are opportunities to improve medication use of adolescents, as for example celebrities with chronic conditions can motivate patients in using their medication and increase their knowledge.[11,12]

[2] Someone who affects or changes the way that other people behave, for example through their use of social media.

Research in adolescents is generally perceived as difficult, as adolescents are a hard-to-reach and hard-to-motivate patient group. The recruitment of patients for the studies in this thesis was indeed challenging, however we achieved relatively large sample sizes. In all studies, we invited adolescents based on their pharmacy prescription records. They received a postal letter from their pharmacy to participate in the study. Adolescents with ADHD were invited to anonymously complete an online questionnaire (***Chapter 3.2***), resulting in a response rate of 15%, without sending a reminder. It probably would have helped to approach them personally.[13] Because based on responses obtained at a high school symposium, we learned that it would have been better to contact respondents personally (data not reported in this thesis). Unfortunately, we did not have access to the contact details of adolescents with ADHD (for privacy reasons).

The response rate within the atopic dermatitis study was 10%. First, we invited around 20 adolescents per pharmacy for the focus groups (***Chapter 3.1***). Thereafter, we tried the suggested personal approach and called all patients who did not respond based on the postal invitation. Despite this personal approach, the response rate was still somewhat lower compared to the ADHD study, probably because adolescents had to be available during a specific time frame. Moreover, focus groups require active participation of patients, thus adolescents should be sufficiently motivated and confident to participate, which might also have negatively affected the response rate.

For the ADAPT study, we invited 1,204 adolescents and the initial response was again low. Therefore we contacted the non-responders by phone (from the pharmacy), which resulted in a response rate of 21% (***Chapter 4***). Many adolescents who received the postal invitation, did not actually read it (in depth), due to the abundance of information, such as informed consent and information leaflets. In the end, 14% of the adolescents we called agreed to participate. The final response rate in the control group was higher (26%) than in the intervention group (16%). Thus the willingness of adolescents to complete two online questionnaires was apparently higher than the willingness to use an app for six months.

During the ADAPT study, we had the impression that participating adolescents were interested in testing our mHealth intervention, though it was not their top priority. Often, participants tended to forget to complete questionnaires or to download the app. Therefore we had to remind patients, successfully resulting in a low drop-out rate of 3.7%. We also attempted to keep our social media (Facebook and Instagram) and website up-to-date, to remind adolescents of the ADAPT study. However, forgetting to participate is an age-specific issue, like they also often forgot to take their medication (***Chapter 3***).

ADOLESCENTS USING CHRONIC MEDICATION

Medication use changes appreciably during adolescence (***Chapter 2***). This is primarily related to changes in the prevalence of diseases over time, e.g. the prevalence of atopic dermatitis, ADHD, and asthma decreases during adolescence.[14-19] However there are also differences within adolescent patient populations, as for example the use of dermatologicals decreased over time in females, while it increased in males (***Chapter 2***). Moreover, there are seasonal variations within patients.[20] All these differences emphasize the need for a personal treatment approach, suggesting that the 'one size fits all' does not apply for adolescents using medication.

Chapter 3 showed differences between adolescents with ADHD and asthma. For example, adolescents with asthma experienced more symptoms and expected a more chronic course of their illness, compared to adolescents with ADHD. However adolescents with asthma were less emotionally upset, their life was less affected by their illness, and they had more personal control over their illness, compared to adolescents with ADHD. The duration of the illness might explain these differences in illness perceptions; most adolescents with asthma were diagnosed with asthma longer ago (i.e. in their early childhood), thus they grew up with it and were used to it, whereas ADHD is often diagnosed during school age or early adolescence. The nature of symptoms and the effectiveness of medication to control these symptoms might also contribute to the difference in illness perceptions. Asthma symptoms are mainly somatic, such as cough and wheezing and can be well controlled with inhaled corticosteroids (ICS). ADHD has psychological symptoms, which are less well defined and the effectiveness of medication is much lower. The differences between adolescent populations, might also be partly related to the type of research used to obtain the data. Adolescents with asthma were recruited for a randomised clinical trial, thus they are likely to be highly motivated, whereas adolescents with ADHD participated in an anonymous survey.

Despite the differences, there were also similarities between the studied adolescent patient populations (***Chapter 3***). For all studied conditions (atopic dermatitis, ADHD, and asthma), adolescents were poorly adherent, i.e. less than 40% was adherent, with forgetting as a main reason. These adherence rates were lower compared to other age populations, which might either suggest that adolescents are less adherent, or that adolescents are more honest about their actual mediation use.[21] Healthcare providers should therefore create an open and honest environment to elicit and discuss both practical and perceptual barriers for adherence. Moreover, they should make sure that adolescents understand their medication regimen and instructions for use,[22,23] as even some adults with asthma still do not know the difference between controller and rescue mediation.[10]

Maintaining adherence in adolescents is complex. Besides forgetting, we found that adolescents with atopic dermatitis had incorrect beliefs about the mechanism of action (***Chapter 3.1***). Moreover, adolescents with ADHD perceived in particular low needs (***Chapter 3.2***). The latter might be related to the perceived effectiveness or experienced side effects of their ADHD medication. A suggestion

to improve adherence for these adolescents is to increase their disease and treatment knowledge and their medication beliefs (***Chapter 3.3***).

Adolescents with asthma already seemed to understand the necessity of their ICS (***Chapter 3.3***), thus the focus should be on increasing unintentional adherence, e.g. prevent forgetting. Healthcare providers should help adolescents to find ways to implement medication routines in their everyday life. Solutions might be to take ICS at other moments than standard at 8am and 8pm and avoid taking it in the classroom. Moreover, improving treatment control (i.e. *how much do you think your medication can help your illness?*) and coherence perceptions (i.e. *how well do you feel you understand your illness?*) might also contribute to improved adherence rates (***Chapter 3.3***).

All studied adolescent patient populations were in general indifferent towards their medication (***Chapter 3***). This indifference might be related to the nature of the disease or effectiveness of the treatment. However indifference is also very age-specific, because during adolescence the parental supervision decreases, while adolescents often cannot overlook long-term consequences. A solution to support a more accepting attitude is to improve the partnership between adolescents and healthcare providers, and to increase patient's knowledge, based on their specific situation and needs.

COMPLEXITY ADHERENCE AND DISEASE CONTROL

Theoretically, the relation between adherence and disease control is clear; appropriate use of medication is expected to result in sufficient disease control and thereby a good quality of life.[24-26] We therefore aimed to improve medication adherence in the ADAPT study, as a substitute parameter to improve disease control (***Chapter 3.3***). Most adolescents with asthma in the ADAPT study actually reported to be non-adherent, thus there was a lot to gain here.

Although we found a relation between adherence and asthma control, it was not very strong (***Chapter 3.3***), indicating that asthma control also depends on other factors than adherence (e.g. inhaler technique, seasonal aspects, lifestyle, and illness perceptions). Moreover, the mechanism of action of ICS might increase the complexity of the relation between adherence and asthma control. Patients are advised to use daily controller medication to suppress their chronic inflammation. However when they sometimes forget to use ICS, they will not directly experience wheezing or other asthma symptoms. This may feed beliefs that ICS are not always needed and that full adherence is not necessary.

We suggest possible 'feedback mechanisms' between disease control and illness perceptions ('treatment control' and 'timeline') and thereby medication beliefs (***Chapter 3.3***). Adolescents may for example accept a certain extent of disease control that is not optimal, but sufficient. This will

make it very difficult to improve adherence and disease control beyond a certain acceptable level. These feedback mechanisms might possibly contribute to the weak correlations (***Chapter 3.3***).

The spontaneous decrease of asthma symptoms during adolescence might also affect adherence and the need to achieve asthma control.[16] Nonetheless, although the total dose of ICS may be reduced, patients still need to use ICS regularly. Moreover, tapering of ICS requires adequate illness insights and medication knowledge. Adolescence might be the proper life phase to develop these skills, however a good therapeutic relationship with their healthcare provider is therefore required.

Remarkably, the majority of adherent adolescents (75%) had still no disease control (***Chapter 3.3***). We measured disease control using the validated Control of Allergic Rhinitis and Asthma Test (CARAT).[27] In clinical practice, the Asthma Control Questionnaire (ACQ) or Asthma Control Test (ACT) are more often used.[28,29] However the ACQ requires a forced expiratory volume (FEV_1) measurement, which was not measured in patients participating in the ADAPT study, and the ACT requires an estimation of the patient's own asthma control, which might be difficult for adolescents without guidance. An advantage of the CARAT is that it focuses on symptoms and contains one additional question on extra medication use. Moreover it distinguishes between asthma and allergic rhinitis symptoms. The latter is important, because nowadays ICS are often inappropriately prescribed for allergies, and uncontrolled allergic rhinitis can contribute to uncontrolled asthma.[30-33]

For further research on adherence and disease control, we suggest direct measurements, because with self-report comes a social desirability bias and under- or overreporting.[34] Objective electronic monitors, such as smart inhalers, are suggested to measure adherence over time. For asthma control, we recommend forced expiratory volume (FEV_1) or regular peak flow measurements, preferably linked to digital diaries (e.g. on a smartphone), because paper diaries are not always reliable.[35,36] Objective digital FEV_1 or peak flow measurements avoid underreporting of asthma symptoms, and might contribute to more awareness, and thereby supports adherence.

INTERVENTIONS IMPROVING ADHERENCE

Improving adherence is about implementing a behavioural change and there may be different reasons underlying non-adherent behaviour. Adherence interventions should therefore contain multiple functionalities. In particular, knowledge (education), self-efficacy (motivation), and awareness (measurements) are important when changing patient's behaviour (***Figure 1***).[37] This is in line with the results described in ***Chapter 3***, because adolescents had an indifferent attitude (low motivation), had incorrect beliefs about the treatment mechanism (education), were insufficiently aware of their poor symptom control (low awareness), and were in general poorly adherent. The complexity of medication adherence might explain why interventions containing only one element were often not effective.[38,39]

To improve adherence effectively, there is a need for a tailored approach based on the type and cause of non-adherence and the specific needs of (adolescent) patients.[4,40] The basic tools to support education, motivation, and measurement are training, goal setting, and medication package (i.e. providing electronic monitoring and information; ***Figure 1***). The ADAPT intervention contained functionalities in line with this (***Figure 1***; *Italic*). Short movies and a pharmacist chat function provided adolescents with knowledge and may motivate them. Questionnaires provided monitoring of symptoms and adherence over time, aiming to increase awareness and motivation, and may contribute to improved disease and treatment knowledge (***Figure 1***). Moreover, we added an age-specific peer chat, and a medication reminder to prevent forgetting. The multiple functionalities of ADAPT enabled adolescents to choose those functionalities that fitted their needs best.

The ADAPT application has the potential to support self-management, which is defined as *"the tasks that individuals must undertake to live with one or more chronic conditions"*. Self-management is affected by different factors, for example by the partnership between patient and healthcare provider, medication beliefs, disease knowledge, illness perceptions, co-morbidities, lifestyle, and social support.[10,41] To ensure effective self-management, patients need to be actively involved in their disease management, which includes being resourceful and careful. This might be hard for an adolescent, who is in the middle of a process to become an independent individual. The different functionalities of the ADAPT intervention aimed to support self-management. For example the pharmacist chat facilitates the partnership between adolescents and pharmacists, and the symptom monitor give patients more insights into their disease.

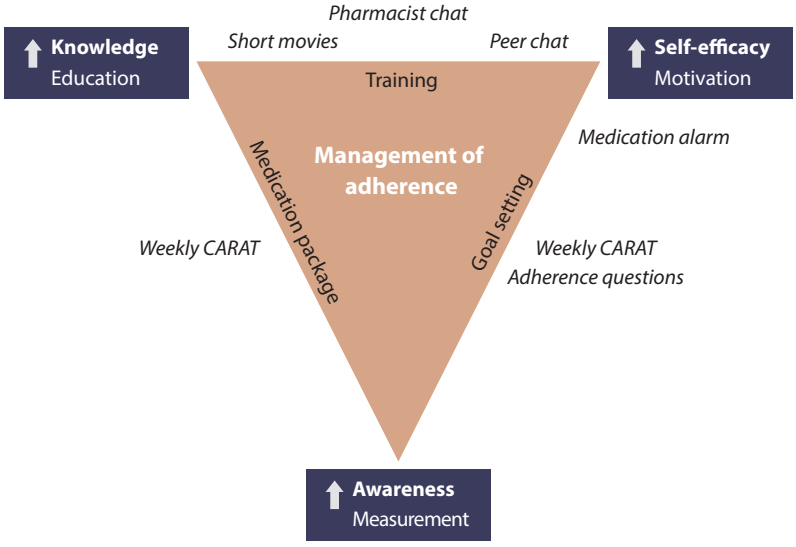

Figure 1. Elements for changing patient's behaviour, with the Adolescent Adherence Patient Tool (ADAPT) functionalities (*Italic*) positioned along the axes (adapted from Vrijens *et al.* 2014).[37]
CARAT, Control of Allergic Rhinitis and Asthma Test.

TAILOR INTERVENTIONS TO ADOLESCENTS

To increase medication adherence during adolescence, a tailored approach is suggested, because as described above adolescents have specific practical and perceptional barriers (***Chapter 3***).[42-44] Shared decision making (SDM)[3] is such tailored approach, which actively involves both the healthcare provider and the patient.[45,46] SDM is a patient-centred model where patients are actively involved.[47] The partnership between patients and healthcare providers supports disease management, including adequate medication adherence.[10,48] Previous studies showed that SDM improved medication adherence, asthma control, and quality of life in patients with asthma.[45,49] Unfortunately, it has been reported that establishing a therapeutic relationship with adolescents with asthma is especially difficult.[10] The interactive ADAPT intervention has the potential to facilitate SDM, because data of the app can be used as input. Moreover, the pharmacist chat function facilitates contact and patients might therefore feel more supported by their pharmacist, even when they are at home.

Most previous developed mHealth interventions were based on the opinion and preferences of clinicians or parents, or were based on literature only.[50] To increase the likelihood of developing an effective tailored intervention, it is important to involve patients from the start. Therefore, we developed the ADAPT intervention (***Chapter 4***) based on extensive patient input.[8] Moreover, the ADAPT intervention was based on a theoretical framework; the Common Sense Model of Self-Regulation (CSM).[51] CSM proposes cognitive and emotional representations towards a health threat, resulting in illness perceptions and medication beliefs which affect health behaviour.

In this thesis, the intervention was delivered by pharmacists, because we focused on medication use, as the primary aim of the ADAPT intervention was to increase medication adherence. Moreover, adolescents infrequently visit the pharmacy, hampering effective medication counselling.[3] The ADAPT intervention provides opportunities to bridge this gap.

EFFECTIVENESS ADAPT INTERVENTION

We carefully developed the ADAPT intervention, grounded in an adequate theoretical model, an involved different stakeholders. However, despite our well-developed intervention, we found no effect of the intervention in the whole study population. Adherence rates only increased in patients with poor baseline adherence rates, especially in those having poor asthma control (***Chapter 4.2***). No effect was found on disease control and quality of life. Previous studies with tailored multicomponent mHealth interventions showed comparable results; adherence increased, while there was no direct effect on clinical outcomes.[38] These findings emphasize the complex relation between adherence, asthma control, and quality of life (***Chapter 3.3***).

[3] Mutual sharing of information to build consensus about preferred treatment that culminates in an agreed action.

We also measured illness perceptions and medication beliefs at start and end of follow-up. The results suggest that these perceptions on illness and medication are relatively stable, as no intervention effects were found (results not shown in this thesis). ***Chapter 3.3*** showed a complex relation between illness perceptions and adherence.[52] In our study population, only 'coherence' and 'treatment control' perceptions were associated with adherence.[53] The questionnaires, short movies, and pharmacist chat could theoretically increase patient's disease and treatment knowledge (***Figure 1***) and thereby improve illness perceptions. However there was little to achieve in the illness perceptions of adolescents with asthma; as they were not emotionally affected by their asthma, they experienced not much symptoms, and they believed they had control over their asthma. Moreover, 'coherence' and 'treatment control' perceptions were already high in our study population (median 8; range 0 - 10), which might explain why no intervention effect was found.

Although there was no intervention effect on medication beliefs, there was a weak correlation between adherence and medication beliefs (***Chapter 3.3***). Pharmacists should be aware that patients often have different views regarding their medication, and they should try to elicit patient's treatment concerns.[54] Adolescents reported no concerns and they had high necessity beliefs, thus there was not much to gain in their medication beliefs, in relation to adherence.

The ADAPT study increased adherence in poorly adherent patients with 10%, which may be insufficient to cause an effect on clinical outcomes. Furthermore ICS has long-term effects, thus there may be a delay in improved disease outcomes via appropriate adherence. Therefore more long-term research is needed in a larger study population to unravel the complex relation between ICS adherence and long-term clinical outcomes. Nonetheless, we should keep in mind that teens with asthma tend to underestimate their symptoms.[26,55] Adolescent often feel alright and do not realise their uncontrolled disease (and thereby their suboptimal treatment; ***Chapter 3.3***). They find ways to deal with their asthma symptoms, for example by refraining from practicing sports, whilst this could still be possible with sufficient asthma control.

E-CONSULTS WITH THE PHARMACIST

Adherence improved significantly in adolescents who used the chat function to contact their pharmacist (***Chapter 4.3***). No effects were found from the other app functionalities. When focusing on patients with poor adherence rates (Medication Adherence Report Scale [MARS] ≤19; n=26), we found that using the pharmacist chat (p=0.046) and the peer chat (p=0.011) contributed independently to an increase in medication adherence.

The peer chat was an age specific functionality aiming to improve the emotional representation of their asthma, it was used by 21% of the adolescents in the intervention group (n=18), and by 19% of adolescents with poor adherence rates (n=5). Those five patients sent on average 13 messages per

person and their self-reported adherence increased from MARS 15 to MARS 22. On the other hand, no changes were found on their emotional asthma representation. The peer chat might therefore have contributed to more asthma engagement, which could have improved adherence.

The pharmacist chat was used by 44% (n=38) of the intervention group, and by 35% of the poorly adherent adolescents (n=9). The aim of the pharmacist chat was to educate and motivate patients (***Chapter 4.1***). The exact mechanism which caused the increase in adherence is unknown, because we only studied physical engagement with the app (i.e. quantity of app use), while there is also psychological engagement with the intervention, which cannot be measured. We believe that patients who used the pharmacist or peer chat were better motivated and involved, and thereby more motivated and prone to improve their adherence.

The pharmacist chat also promoted communication between patients and pharmacists (***Chapter 5.1***). Patients could ask for help when needed, and pharmacists could answer at convenient moments. Additional analysis showed that sending multiple messages is only related to the increase in adherence (p=0.046). Thus we suggests that the pharmacist chat improved the partnership between patients and pharmacists and therewith contributed to the increase in medication adherence (in line with SDM).[56,57]

The educational part of the pharmacist chat might also have contributed to improvements in medication adherence, because most patients who started the chat conversation (n=12) posed a question concerning their medication (n=5) or the app use (n=4). The pharmacist's answer could have improved their (medication) knowledge, and thereby adherence. In four cases, patients did not receive an answer of their pharmacist, which inhibits further implementation (***Chapter 5.2***). However, most pharmacist were generally actively involved; 68% of the chat conversations was started by pharmacists and the majority of participating pharmacist (82%) sent messages to the their patients. For further implementation it is important that pharmacists continue to support the use of the intervention (***Chapter 5.2***). More research is needed towards effective ways of contacting patients through mHealth and the optimal intensity of feedback.

Chatting with patients is new for pharmacists, nonetheless the participating pharmacists highly appreciated the electronic consults (e-consults). Pharmacists recommended to introduce mHealth also for other patient populations, such as older patients with diabetes, COPD, or cardiovascular disease (***Chapter 5.1***). Previous studies using digital communication methods showed already positive effects in those populations. For example studies in diabetic patients showed that a healthcare provider chat is important to achieve clinical effectiveness.[58] Also telephone counselling was shown effective in improving medication adherence.[59] These findings, combined with our results, suggest that e-consults (in combination with face-to-face counselling) have the opportunity to improve healthcare of patients.

Currently not many mHealth interventions are designed for use in a pharmacy setting,[60-62] while positive effects of pharmacy delivered mHealth interventions are shown in this thesis and other studies.[63-65] In general, community pharmacists seem well positioned to support medication use, because medication counselling is their responsibility and pharmacists were regarded as more easily accessible (***Chapter 5.1***).

INTEGRATED CARE

The studies described in this thesis showed opportunities for pharmacists to improve patient's disease outcomes. In the ADAPT study, we focused on pharmacists as healthcare providers and the mHealth intervention delivered tools to pharmacists to provide extra care. The latter fits with the international trend of a more clinical role for pharmacists.[2] However, increasing the healthcare providing role of pharmacists, might affect the physician's role. For example, physicians may prescribe less medications.[66] Thus increased collaborations between pharmacists, physicians, and other healthcare providers are suggested when implementing mHealth in the pharmacy.

As illustrated, the ADAPT intervention contributes to the integrated care trend, which is defined as *"The organisation and management of health services so that people get the care they need, when they need it, in ways that are user friendly, achieve the desired results, and provide value for money"*.[67] Integrated care settings can offer advantages for both, patients (better outcomes) and healthcare providers (lower workload). Physicians could identify uncontrolled patients, and pharmacists can subsequently verify adherence based on dispensing data and self-report. This way, pharmacists and/or physicians may offer patients tailored support with their medication use. Ideally both physicians and pharmacists should have insights in the app data to support integrated care.

Continuity of care is important for patients,[7,68] however during late adolescence, the care for patients with chronic conditions shifts from paediatricians to adult oriented healthcare. During this transition, relationships, access, beliefs, knowledge, and skills are important.[7] The pharmacist and GP often stay the same. Thus the ADAPT intervention can play an important role here, as it promotes contact with healthcare providers, and thereby supports the continuity of care during the transition.

MHEALTH SUPPORTING MEDICATION USE

This thesis confirms that mHealth is an attractive way to support patients with their medication use. It is accessible, relatively inexpensive, can be tailored to patient's needs and preferences, and can contain several functionalities targeting different aspects of non-adherent behaviour.[60,61,69] Additionally, it fits with the ongoing digital revolution, as nowadays 70% of the people in Western Europe own a smartphone.[70]

Because of its potential, the field of mHealth is rapidly developing with more than 300.000 available health apps. The mHealth development industry is one of the fastest growing industries and the most attractive mHealth sector is 'connection to your doctor'. However, this rapid development also comes with some problems. Most mHealth apps are infrequently used by patients, based on ideas of individual healthcare providers (or patients), and/or not properly evaluated.

For researchers it is impossible to catch up with the rapid development of mHealth. For example, we conducted a randomised controlled trial, which is currently the most reliable form of scientific evidence. However the preparation of ethical approval of such a study could easily take a year, while in one year more than 50.000 new health apps come available with new and more advanced functionalities. Moreover explanatory trials may not be best suited to evaluate complex interventions in dynamic environments. Therefore other ways to evaluate digital interventions are needed, to promote the development of mHealth. Mobile applications with different functionalities could be evaluated in large pragmatic observational studies, to obtain more insight in the use and long-term effects (>1 year) of mHealth. Alongside this, qualitative work will give additional insights in how patients use applications and how these can be improved. This would render mobile applications that are continuously evaluated and provide valuable insights in the way patients manage their disease.

The large amount of currently available mHealth apps and the lack of evidence is also a problem for patients. They need help to select the right app, as patients can't see the wood for the trees. To illustrate; there are more than 200 apps available focusing on improving asthma care.[71] Different initiatives regarding quality marks are being developed, for example the iOS App Store has its own approval procedure, which is about the general quality of the app. Other platforms, such as Google Play, have not yet implemented such criteria. Therefore new initiatives that support patients to choose the right app are needed, such as a selection assistance tool for health apps.

Given the large availability of promising local mHealth initiatives, we do not believe that we need to develop new mHealth functionalities. Ideally, all mHealth developers should work together to evaluate different functionalities in different patient populations. This should result in generic mHealth applications that patients may adapt to their personal situation. This could particularly be useful for patients with several chronic conditions. Ideally, the most suitable and reliable apps for patients should become automatically available based on data derived from wearables.

If patients would have the perfectly tailored app, the next question is: how could they implement it in their daily life? The smartphone is already the constant companion of most people, and people increasingly use their smartphone as their primary device for online access at home.[72] However it is difficult to implement a new app in everyday life. Consumers use on average nine different apps on a daily basis, while more than 80 apps are installed on their smartphone. The most popular app categories are utilities and tools (e.g. weather, banking), social networking (e.g. Snapchat), communication (e.g. WhatsApp), and productivity (e.g. to-do lists).[73]

Another question is: how could long-term use of mHealth interventions be stimulated? The ADAPT study showed already that an app is differently used per person and that the use varied over time (***Chapter 4.3*** and ***Chapter 5.1***). In general, 25% of app users only use an app once. Health status, usability, accessibility, utility, and motivation are suggested to be important for long-term mHealth use.[74] Thus to improve patient's engagement with mHealth apps, fast and reliable apps are needed, and the first experience with the app should be positive. Additionally, apps for adolescents should be up-to-date and should contain (constantly) new content, as adolescents easily get bored.[75]

The normalization process theory, used in ***Chapter 5.2***, described how mHealth can get routinely embedded in everyday practice.[76] We state that the implementation of mHealth in daily life is a complex continuous process, where sense-making, effort, commitment, and appraisal should be clear. Moreover, it is about time for action.[77] All healthcare providers should combine forces and start to use mHealth routinely, because if healthcare providers systematically offer mHealth to support patients, it is possible to implement mHealth in everyday life.

CONSIDERATIONS MHEALTH

Along the numerous positive effects and opportunities of mHealth, there are also several disadvantages. As mentioned above, continuous support is needed to further implement mHealth in clinical practice (***Chapter 5.2***). Thus for an interactive app with intensive patient contact, healthcare providers should be available to assist patients and to answer questions, which is not possible in the current healthcare system. Nowadays most mHealth initiatives are performed in addition to regular duties of healthcare providers. For further implementation, mHealth should be routinely integrated with regular tasks of healthcare providers, for example physicians should alternate face-to-face consults with e-consults.

In addition, advanced and stable 4G networks are needed for mHealth, which can currently be a constrain in remote areas. Digital bugs can also be a problem, as they can hinder further implementation. Bugs should therefore be solved quickly, for example by creating app updates. Thus, besides continuous healthcare provider support, there should also be continuous technical support. App developments are needed to improve the app, otherwise users get annoyed, which will hinder further implementation. And last but not least; patients should be actively involved, as they should download the updates and have to ensure enough available space on their phone.

MHealth privacy and ethics

With digital innovations, privacy is a major concern, in particular when it comes to healthcare data. Many patients and healthcare providers are worried about their privacy and safety when it comes to digital innovations. A good example can be found during the (failed) implementation of the

electronic patient file (EPD), when 50% of the Dutch population suddenly became interested in their privacy protection.[78]

The EU General Data Protection Regulation (GDRP), which became active on 25 May 2018, aims to improve the protection of personal data and to ensure equal protection across Europe. For example, organizations need to explain why they collect personal data, where they use it for, and what the duration of data storage is. Additionally, citizens should be given access to the data on request.[79] Thus data of patients is now increasingly protected, not only in clinical trials, but also in everyday life.

Secure mobile connections are also important to ensure patient's safety. These connections already exist, for example in banking apps. This suggests that privacy and security should not be a major issue anymore. For example in the ADAPT study, all (personal) app data were encrypted and securely saved (***Chapter 4.1*** and ***Chapter 4.3***).

Next to privacy and safety, are the potentially underestimated ethical aspects of mHealth. There are three major ethical issues concerning the implementation of mHealth: (1) data ethics, (2) accessibility of digital health, and (3) the effect on patient-healthcare provider contact.[80,81]

1. New technologies provide the opportunity to share large amounts of information, creating big data[4]. Data-driven healthcare seems promising, but a lot of data in itself does not imply good healthcare. Moreover, this strictly personal data brings risks of unethical profiling of patients.
2. MHealth cannot be used by everyone. Some applications are not available on all smartphones, not user friendly, or they do not match with the patient's knowledge or digital skills. Moreover, some people cannot afford a smartphone.
3. MHealth is related to issues involving direct contact with healthcare providers, for example; should patients or healthcare providers use e-consults when they are available? And should they additionally receive face-to-face care?

MHealth may also contribute to medicalization of patients, because by using mHealth, patients can continuously be aware of their chronic condition. This might result in obsessive behaviour, as has been described for obsessions with healthy eating (i.e. orthorexia). Moreover, if all details of patients are registered via mHealth, it also create dilemma's for healthcare providers. For example, if patients stay up late or drink too much alcohol, do healthcare providers have to act on this information? Clearly, mHealth is accompanied with unique ethical issues and ethical guidelines in this field should be developed.[82]

[4] Extremely large data sets that may be analysed computationally to reveal patterns, trends, and associations, especially relating to human behaviour and interactions.

Cost-effectiveness

Reimbursement will promote the normalization of ADAPT (***Chapter 5.2***), however payers expect that the cost-effectiveness of mHealth interventions is investigated. There should be a balance between costs and efficiency gains. For asthma patients, improved disease management and medication adherence could result in decreased use of bronchodilators, less exacerbations and hospitalizations, less regular consultations, and from a societal perspective less (school) absenteeism. Hence there can clearly be a reduced cost benefit. The required investment for the mHealth intervention (***Example 1***) should be formally compared with these potential realizable cost benefits. Subgroup analysis may identify patients (e.g. with poor adherence rates) in whom mHealth is especially cost-effective.

Example 1. Costs of the ADolescent Adherence Patient Tool (ADAPT) mHealth intervention

In total, 6% of the Dutch adolescents is diagnosed with asthma (while 12% experienced asthma symptoms), which are 85,545 adolescents.[83,84] There are 1,989 community pharmacies in the Netherlands,[85] thus on average 43 adolescents with asthma per pharmacy. According to the developers, ADAPT will costs €750 per pharmacy per year, i.e. €17.44 per adolescent per year. To put this in perspective, the price of inhaler instructions is €17.17.

Pharmacist have to counsel patients through the app. In the ADAPT study on average three patients per pharmacy participated, and pharmacists spent on average five minutes per week on the intervention (***Chapter 5.1***). Thus for 43 adolescents, pharmacists will spend 72 minutes per week on the intervention, which represents €123.60 per week,[86] resulting in €149.47 per adolescent per year.

The total asthma care costs for patients age 12 - 18 years are €29.3 million per year, hence €342.51 per adolescent asthma patient.[87] Adding the mHealth costs (17.44 + 149.47 = €166.91) to asthma care, results in a total of €509.42 per adolescent per year. However we should keep in mind that patients do not constantly need support,[88] thus the support of pharmacists is probably less time consuming.

IMPLEMENTATION OF ASTHMA MHEALTH IN CURRENT PRACTICE

Many aspects of healthcare can be further digitalized in the future, from consult to pharmacy (***Case 1***). There will be less need for physical hospital and general practitioner visits, as healthcare providers can monitor patients throughout the year, and e-consults can be conducted when needed. Smartphones will be used as health monitors; they will track the health state of patients and signal deviations. Healthcare providers can recall the medical history of their patients remotely, and can urgently provide advice or feedback. Thus with the implementation of mHealth in clinical practice, healthcare will become more personalised, and the focus of healthcare will shift more from curing to preventing, based on the advanced monitoring systems.[89]

Case 1. Mobile health fiction?

Patient B. was diagnosed with asthma during his childhood. Now he is 14 years old, and he manages his asthma using his wearables and smartphone app. This app reminds him of his inhaler. This alert is linked to his smart inhaler and keeps popping up until he uses his inhaler. This smart inhaler also evaluates his inhaler technique. Though it may have been annoying at first, his inhaler technique improved, causing him to experience less asthma symptoms.

With another device linked to his smartphone he measures his FEV_1 and peak flow. Peak flow scores are now constantly above 500 L/minute. All app data (adherence, inhaler technique, peak flow, etc.) are merged with data from his activity tracker, and automatically saved in his electronic patient file, containing all his health-related information. This file is accessible by all involved healthcare providers, which facilitates his asthma treatment, as he does not have to repeat the same story at every healthcare provider.

At first, patient B. also received movies about asthma medication on his app, and he used the Snapchat look-a-like functionality to contact other patients with asthma to share experiences. The app also integrates weather information, such as pollen and smog measurements, and it tells B. when he needs to take his antihistamine. *"The best thing of my app self-management is that I don't have to go to the hospital anymore".* B. attends an e-consult twice a year using his smartphone camera, and for other questions he contacts his pharmacist or physician via the chat function in the app. The partnership with his healthcare providers is thereby improved.

His pharmacy automatically prepares a new amount of his inhaler, two weeks before the previous one is out of stock. Currently, B. has good asthma control and he is adherent, therefore his physician suggested to decrease the ICS dose, which is managed by his pharmacist.

To turn to above sketched case into reality, drastic changes are needed. First of all, more evidence for mHealth is needed. MHealth has the potential to empower asthma patients with valuable tools and skills for monitoring their symptoms, and thereby improving inhaler use and treatment adherence.[90] Currently, not many studies showed clear evidence for mHealth interventions improving adherence rates sufficiently.[60,90-94] In the ADAPT study, there was only a slight increase in medication adherence in patients with poor adherence rates (***Chapter 4.2***). The clinical relevance of the ADAPT intervention on disease outcomes and adherence is therefore limited.

Secondly, healthcare providers, payers, patients, app developers, and policy makers should work together to build an intervention that can be tailored to the needs of different patients with different conditions. Thereafter, mHealth should be supported by all healthcare providers, payers, and policy makers. Thus a new healthcare system which integrates all patient data is needed.

Thirdly, our findings suggest that mHealth is not a solution for everyone. Healthcare providers should therefore tailor interventions to patients who need it most, i.e. patients with low adherence rates. The latter is supported by the eHealth-monitor, as their main message is 'consciously choose eHealth', suggesting to consider if patients really need a mHealth application.[95] Thereafter, patients (and healthcare providers) should trust new digital innovations, which seems already promising, as

the feasibility of acceptability of mHealth is high.[96] However, some people might need more help with implementing mHealth, than others.

Lastly, the implementation, embedding, and integration (i.e. normalization) of mHealth is a complex and continuous process, which is completely described in ***Chapter 5.2***. Until now, no mHealth interventions have been successfully implemented in healthcare. To place the implementation of mHealth in perspective: the fax[5] is still widely used in healthcare to exchange information.[97] Changes beyond individual healthcare providers are needed to normalize mHealth in clinical practice, such as support of professional bodies, use of product champions (i.e. key participants), and appropriate reimbursement models.[64]

The Dutch Healthcare Authority (NZa) publishes a yearly guideline for eHealth funding. Their main goal is to create possibilities to deliver healthcare closer to the patient's home. The expectation is that hospital based telemonitoring of patients is going to be a reimbursable product in 2019. Moreover, GP's are allowed to reimburse a tele-consult with a comparable rate to a face-to-face consult, which might drive the implementation of mHealth forward. Additionally, insurance companies stated that they would like to stimulate several eHealth initiatives.[98]

Opportunities for mHealth

We will see what the future holds, and if healthcare is ever going to be completely digitalized. However at this moment there are already initiatives available of which no one would ever thought of, such as an eNose which can easily diagnose asthma,[99] and smartphone camera lenses which can accurately measure heart rates.[100] Progressive connectivity technologies, such as Bluetooth and Near Field Communication are also promising for healthcare. Moreover, new techniques such as artificial intelligence[6] and blockchain[7] are gaining ground, which might turn medical fiction into reality. Thus the future of mHealth has already started.

In this thesis we show opportunities for the implementation of mHealth supporting medication adherence. The ADAPT intervention was effective in poorly adherent patients (***Chapter 4.2***), the pharmacist chat was effective in the total population (***Chapter 4.3***), it was positive evaluated by patients and pharmacist (***Chapter 5.1***), and the ADAPT intervention has the potential to become normalized (***Chapter 5.2***). In line with the Normalization Process Theory (NPT), we recommend to actually start using mHealth in clinical practice.[101]

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[5] Derived from telefacsimile, which is defined as *"(a copy of) a document that is transmitted electronically along a phone line and is then printed on paper"*.

[6] Theory and development of computer systems able to perform tasks, normally requiring human intelligence, such as visual perception, speech recognition, and decision-making.

[7] Public register in which transactions between two users belonging to the same network are stored in a secure, verifiable, and permanent way. The data relating to the exchanges are saved inside cryptographic blocks, connected in a hierarchical manner to each other. This creates an endless chain of data blocks that allows you to trace and verify all the transactions you have ever made.

METHODOLOGICAL CONSIDERATIONS

We focused on mHealth and medication adherence of chronic patients in this thesis, thus we looked at the 'implementation phase' of adherence, which is defined as *"the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen"*.[102] Pharmacy refill records are the most preferred method to assess implementation. Unfortunately this data was not available for the ADHD patients. In the ADAPT study we were not able to use pharmacy refill records, because the study period consisted of six months and refill records are more reliable over longer time periods.[103] Therefore we used the validated MARS questionnaire to measure self-reported adherence (***Chapter 3.2*** and ***Chapter 3.3***).[104-108] Self-report is a low-cost measurement, which is efficient, easy to perform, and commonly used.[109] Moreover, it provided information about the type of non-adherent behaviour (intentional or unintentional).

Self-report has also some limitations; social desirability bias and under- or overreporting. However as already mentioned in ***Chapter 1***, there is no gold standard of measuring medication adherence.[110] Unfortunately MARS is only validated in adults, and it is shown to be inaccurate for measuring adherence in children with asthma (age 2 - 13 years).[111] However, parents complete these questionnaires for their children, which might cause to the inaccurateness in younger children. Self-report seems suitable for adolescents, as they often report low adherence scores, suggesting no social desirability bias. However, research toward the validation of MARS in the adolescent population is lacking. Therefore research is needed to critically revise the thresholds for adolescents,[112] by for example comparing the MARS score with pharmacy refill records or digital adherence measurements in adolescents.

Illness perceptions and quality of life can only be measured by means of self-report, therefore we used the validated Brief Illness Perception Questionnaire (Brief-IPQ),[113] and the Paediatric Asthma Quality of Life Questionnaire (PAQLQ).[114] The PAQLQ is validated for children aged 7 - 17 years and is previously used in adolescents with asthma.[115,116] The Brief-IPQ measures comprehensibility, and cognitive and emotional illness representations. We excluded the causes item in our analyses, because 41% of the asthma patients (n=96) did not complete this item, which either implies that the cause item was unclear, or that adolescents often do not understand the cause of their chronic illness.

Patients and pharmacists in this thesis voluntary participated and might be more motivated and positive toward mHealth and e-consults compared to those that did not participate. We could have included solely poorly adherent patients for the ADAPT study, as there is less to achieve in patients who are already adherent. However we included the general adolescent asthma population regardless of their adherence or disease control, because the aim was to evaluate the effectiveness in real world diversity,[117] in order to identify patient groups who benefit most. Other studies can use the findings described in this thesis to improve their interventions.

CONCLUSIONS

Adolescents with chronic conditions are a unique patient population, who require special attention of healthcare providers. A personal and tailored approach is suggested, as adolescents have specific needs and preferences, and their adherence to treatment is often poor. Healthcare providers should create an environment in which adolescents can discuss their medication (non-)use without judgements. They should also help adolescents to find ways to implement medication routines in their everyday life. Shared decision making, with special attention for problems and issues relevant for adolescents, might benefit the communication and might increase adolescents' knowledge and motivation, which supports medication adherence. For patients having poor medication adherence, a tailored mHealth intervention is suggested with multiple functionalities. In particular a symptom monitor and the possibility to chat with healthcare providers (in our case the pharmacist) may be beneficial. To further implement mHealth in the pharmacy (or in healthcare), it is important to routinely use mHealth in daily clinical practice.

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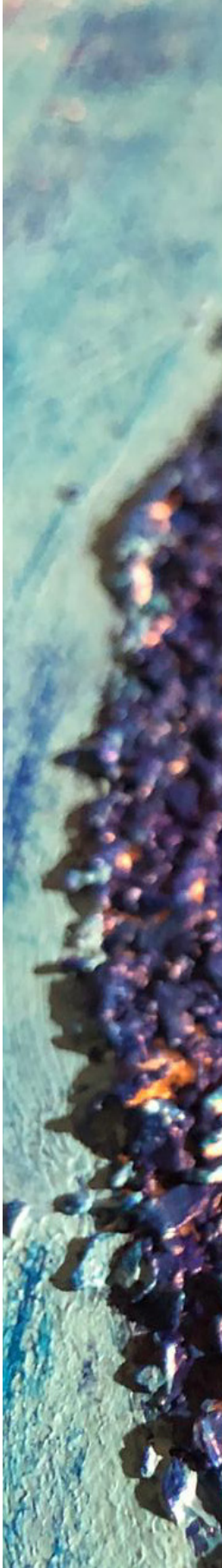
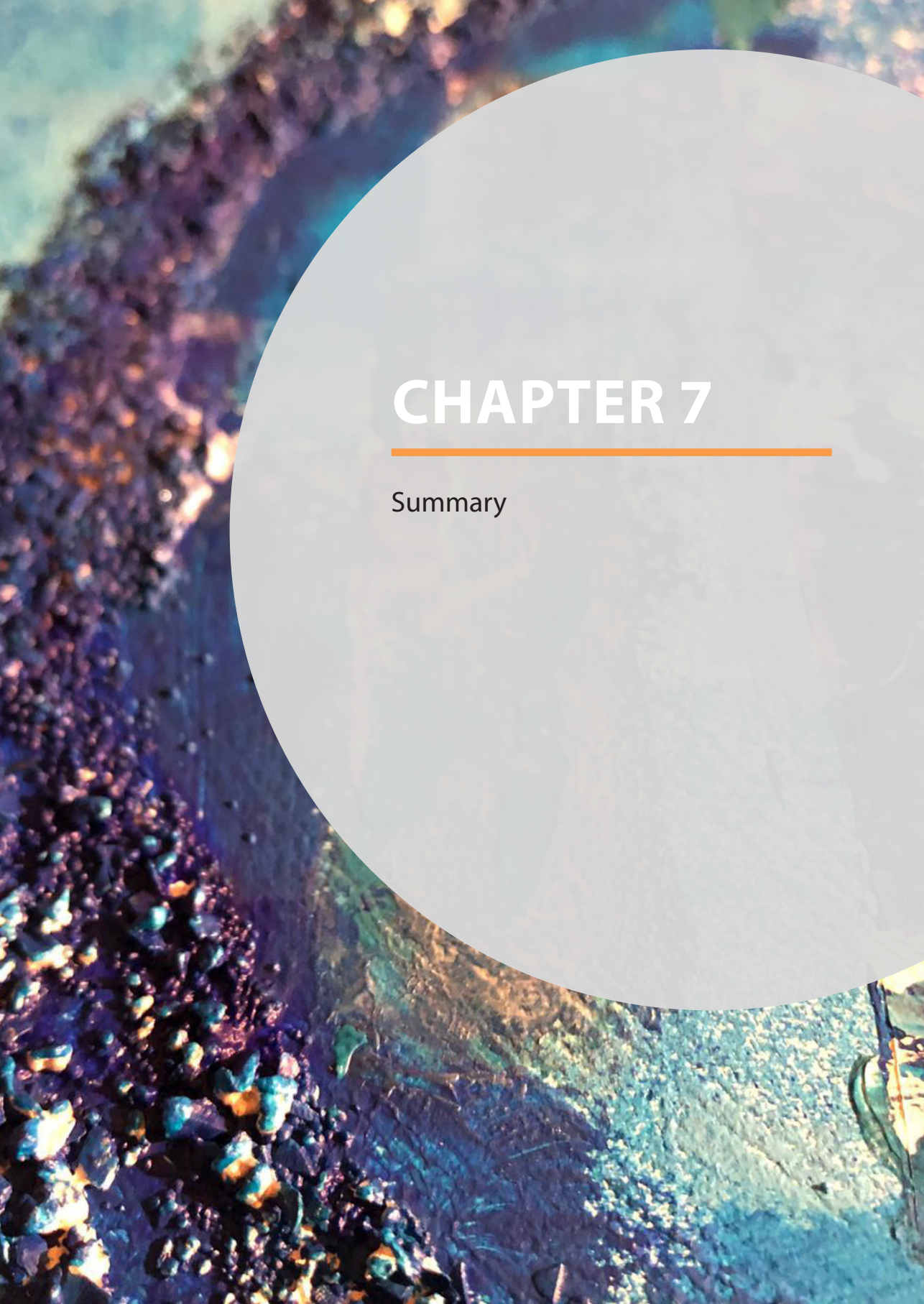




CHAPTER 7

Summary

INTRODUCTION

Adolescence (age 12 - 18 years) is a life phase where many physical, psychological, and social changes occur. Having a chronic illness has a major impact on adolescent's life, as for example daily medication is needed for prolonged periods. Until now, not much is known about medication used of adolescents, as most studies do not distinguish between children and adolescents. It is important to know what kind of medication is used by adolescents in order to have a better understanding of their healthcare utilisation and needs. Moreover, more insights in adolescents' perspectives on their chronic medication are needed, as their perspectives can affect medication use later in life.

Medication adherence is important to obtain optimal treatment outcomes. Unfortunately, non-adherence is a major problem, in particular during adolescence, because age-specific issues play a role and non-adherence rates increase during this life phase. Mobile health (mHealth) interventions might be suitable to increase adherence rates of adolescents, because most adolescents own a smartphone and they have a positive attitude towards mobile technology. In particular, pharmacy based mHealth interventions might be useful, as adolescents rarely visit the pharmacy and pharmacists can act as a medication counsellor. However, currently not many (pharmacy based) mHealth interventions are developed for adolescents.

The overall aim of this thesis was to study adolescents' perspectives on chronic medication use, and to evaluate the effect of a pharmacy-based mHealth intervention to support adherence and self-management in adolescents with a chronic condition.

MEDICATION USED BY ADOLESCENTS

In ***Chapter 2*** we studied medication use of adolescents (N=79,398) using pharmacy dispensing records. More than half of the adolescents (59.7%; N=47,421) collected at least one prescription during adolescence. Half of these adolescents collected prescriptions for dermatologicals (49.3%), followed by medication for the respiratory system (41.8%), and anti-infectives for systemic use (35.3%). The percentage of females collecting at least one prescription was significantly higher compared to males, for almost all therapeutic groups, except for medicines for the respiratory system, nervous system, sensory organs, and systemic hormonal preparations, excluding sex hormones and insulins. During adolescence, the percentage of males using dermatologicals slightly increased, while the percentage of female users decreased with age ($p<0.001$). The highest number of prescriptions were for the nervous system, respiratory system and dermatologicals, and the most frequently collected drug was methylphenidate.

ADOLESCENTS' PERSPECTIVES ON CHRONIC MEDICATION USE

In ***Chapter 3*** we explored perspectives of adolescents towards their medication use. We focused on the most common chronic conditions as described in ***Chapter 2***: atopic dermatitis, attention-deficit/hyperactivity disorder (ADHD), and asthma.

First, in ***Chapter 3.1*** we explored the beliefs, experiences, and preferences of adolescents with atopic dermatitis towards their treatment. Adolescents (age 15.3 ± 2.1 years) in this qualitative focus group study were satisfied with the efficacy of their treatment, but they preferred a faster and more persistent effect. Most adolescents had little contact with their physicians and did not completely adhere to the prescribed medication regimen; they developed their own routine of using topical corticosteroids. They also seemed to have incorrect beliefs about the mechanism of action. Some practical suggestions were mentioned to improve medication use, such as a faster dermal absorption, other (easier) packaging, and follow-up visits with the physician. Based on these findings, we concluded that healthcare providers should devote special attention to adolescents with atopic dermatitis to make them more aware of the principles of topical treatment and to ensure proper use.

The aim of ***Chapter 3.2*** was to gain more insights into the attitudes of adolescents using ADHD medication. We conducted a cross-sectional study with 181 adolescents (age 14.2 ± 1.7 years). Methylphenidate was the most used medicine (92.3%; n=167). More than half of the adolescents (51.4%; n=93) experienced side effects, such as decreased appetite and sleep problems. Most adolescents (82.9%; n=150) had an indifferent drug attitude (perceived low necessity and low concerns) and more than half of the study population (61.3%; n=111) reported to be non-adherent. Remarkably, adolescents scored high on treatment control perceptions. Based on those results, we recommended regular counselling and monitoring of the pharmacological treatment of adolescents with ADHD.

In ***Chapter 3.3*** we focused on adolescents with asthma. We studied the associations between illness perceptions, medication beliefs, medication adherence, disease control, and quality of life. Data of 243 adolescents (age 15.1 ± 2.0 years) who participated in the ADolescent Adherence Patient Tool (ADAPT) study (***Chapter 4***) were available for this cross-sectional study. More than half of the adolescents (62.1%; n=151) were non-adherent, 77.4% (n=188) had uncontrolled asthma, 42.8% (n=104) reported high necessity, and 95.5% (n=232) perceived low concerns about their asthma medication. There was a strong correlation between asthma control and quality of life (r=0.74). Illness perceptions and adherence were correlated with asthma control and quality of life, with the strongest correlation between identity (perception of symptoms) and quality of life (r=-0.66). Medication beliefs were only associated with adherence (r=0.38). We suggested a role for feedback mechanisms and we concluded that influencing illness perceptions and adherence (via medication beliefs) may subsequently improve disease control and quality of life.

MOBILE HEALTH INTERVENTION FOR ADOLESCENTS WITH ASTHMA

In ***Chapter 4*** we focused on an interactive mHealth intervention for adolescents with asthma to support self-management and adherence. We developed the ADAPT intervention based on the needs and preferences of adolescents. The complete rationale and design of the ADAPT study are described in ***Chapter 4.1***. The ADAPT intervention consisted of a smartphone application (app) for patients which was connected to a desktop management system for pharmacists. The app contained several functionalities to improve adherence: (1) a questionnaire to monitor symptoms over time, (2) medication alarm to prevent forgetting, (3) short movies to educate patients, (4) peer chat to facilitate contact with peers, and (5) a pharmacist chat to facilitate contact between adolescents and healthcare providers. Additionally, (6) questions concerning adherence appeared in the app every two weeks. The ADAPT intervention is evaluated in a cluster randomised controlled trial in 66 community pharmacies, where the intervention group had six months access to the intervention. Asthma patients aged 12-18 years were invited to participate and adherence was measured using the self-reported Medication Adherence Report Scale (MARS).

In total, 234 adolescents (age 15.1 ± 1.9 years) completed the ADAPT study (***Chapter 4.2***). No intervention effect was observed on adherence in the total adolescent asthma population (p=0.25), however adherence rates increased in non-adherent adolescents (n=76; intervention effect +2.12; p=0.04). This intervention effect was even stronger in non-adherent patients with uncontrolled asthma at baseline (n=74; intervention effect +2.52; p=0.02). No effect was observed on asthma control or quality of life. Based on these results, healthcare providers could consider a tailored mHealth approach to improve asthma treatment of adolescents.

In ***Chapter 4.3*** we explored the use and effective engagement of adolescents with the ADAPT intervention. All app usage was securely registered in a log file and showed that 86 adolescents (age 15.0 ± 2.0 years) used the ADAPT app for 17 times on average (range 1 - 113) per person. On average three different functionalities were used, and 13% of the adolescents (n=11) used all functionalities of the app. The most used functionalities were the questionnaires to monitor symptoms and adherence, thereafter the movies, pharmacist chat, and peer chat. Females used the app more often than males (p=0.01), and for a longer periode of time (p=0.03). The total app usage did not affect adherence, however use of the pharmacist chat positively affected medication adherence (p=0.01). We suggested that mHealth applications for adolescents with asthma should contain different functionalities. Suggested key functions to promote use and effectiveness of mHealth are questionnaires to monitor symptoms and a healthcare provider chat.

IMPLEMENTATION OF MHEALTH IN THE COMMUNITY PHARMACY

Chapter 5 covers the further implementation of mHealth interventions in the community pharmacy. Process evaluations are important for further implementation, therefore we evaluated the ADAPT intervention in ***Chapter 5.1***. Pharmacists and patients perceived many beneficial effects and were positive about the ADAPT intervention. Most patients (78.0%; n=64) would recommend the ADAPT intervention to others, and agreed that the pharmacy was the right place for providing treatment related information (63.4%; n=52). The possibility to monitor asthma symptoms was highly appreciated by patients and pharmacists. Pharmacists were satisfied with ADAPT (95.7%; n=22), and using the intervention was not time consuming (91.3%; n=21). The ADAPT intervention promoted contact with patients (73.9%; n=17) and facilitated the healthcare providing role of pharmacists (82.6%; n=19). Pharmacists who did not have access to the ADAPT intervention mentioned time constraints and funding as main barriers for using mHealth. This evaluation study emphasized the opportunities for mHealth to improve the quality of care, which supports the need for further implementation in clinical practice.

Getting a new intervention into routine practice (i.e. normalization) is a complex and continuous process. Therefore we assessed the normalization potential of the ADAPT intervention in ***Chapter 5.2***, by applying the Normalization Process Theory (NPT). NPT is a sociological action theory, which explains factors that promote or hinder implementation, embedding, and integration of new interventions in clinical practice. Pharmacists understood the purpose of ADAPT and were prepared to undertake the necessary work of implementation; however, the time required to implement the intervention was a significant barrier in the absence of appropriate reimbursement mechanisms. The potential for normalization could be enhanced by the use of product champions and appropriate reimbursement, to ensure the participation of pharmacists. Support from professional bodies for the use of mHealth would also promote normalization. Thus the ADAPT intervention has the potential to be normalized in the community pharmacy, however full normalization would require changes in pharmacy practice and reimbursement models.

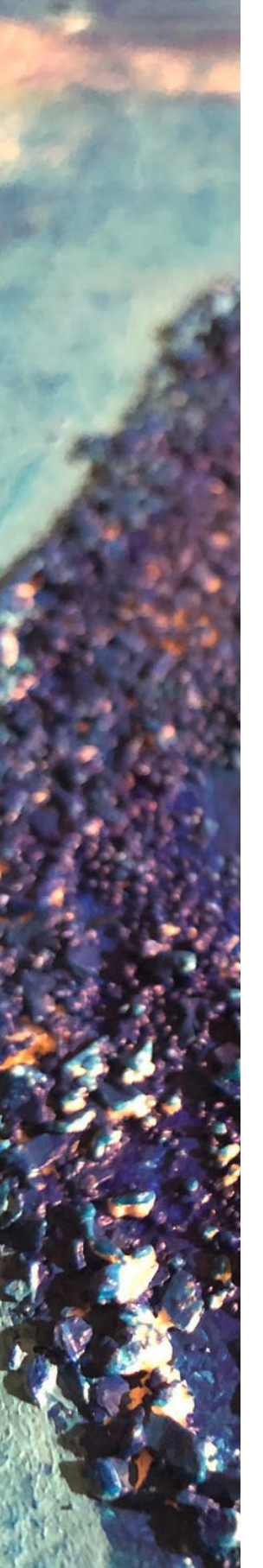
GENERAL DISCUSSION

In ***Chapter 6*** we summarized the main findings, we discussed adolescents in healthcare, and we elaborate on the perspectives of adolescents using chronic medication. We also discussed the adherence problem and interventions supporting adherence, including the ADAPT intervention, thereafter we placed our findings in a broader perspective and described opportunities for mHealth in the pharmacy and beyond. We considered different aspects related to mHealth, for example the cost-effectiveness, and we considered methodological aspects of our studies. In the end, we provided recommendations for effective use and further implementation of mHealth and we described implications for further research.

We concluded that adolescents with chronic conditions are a unique patient population, who require special attention of healthcare providers. A personal and tailored approach is suggested, as adolescents have specific needs and preferences, and they are poorly adherent. A tailored mHealth intervention with multiple functionalities is suggested for non-adherent adolescents, in particular a symptom monitor and the possibility to chat with a healthcare provider may be beneficial. To further implement mHealth in the pharmacy (or in healthcare), it is time to routinely use mHealth in daily clinical practice.

CHAPTER 7

Samenvatting



INTRODUCTIE

Adolescentie (leeftijd 12 - 18 jaar) is een levensfase waarin veel lichamelijke, geestelijke, en sociale veranderingen plaatsvinden. Een chronische ziekte heeft een grote invloed op het leven van adolescenten. Patiënten moeten bijvoorbeeld voor langere tijd medicatie gebruiken. Tot nu toe is er niet veel bekend over het medicatiegebruik van adolescenten, want de meeste onderzoeken maken geen onderscheid tussen kinderen en adolescenten. Het is belangrijk om meer te weten te komen over het medicatiegebruik van adolescenten, omdat we daarmee een beter inzicht krijgen in het zorggebruik en de behoeften van adolescenten. Bovendien zijn er meer inzichten nodig in het perspectief van adolescenten op hun geneesmiddelgebruik, want dit perspectief kan het medicatiegebruik op latere leeftijd beïnvloeden.

Therapietrouw is belangrijk voor de optimale werking van een geneesmiddel. Helaas, zijn veel patiënten niet-therapietrouw en dit is een groot probleem. Gedurende adolescentie wordt dit probleem extra ingewikkeld; de therapietrouw neemt verder af en leeftijdsspecifieke issues, zoals vergeten, spelen een rol. Mobile health (mHealth) interventies zijn wellicht geschikt om de therapietrouw van adolescenten te verbeteren, want de meeste adolescenten hebben een smartphone en ze staan positief tegenover mobiele technologie. MHealth interventies waarmee adolescenten direct contact kunnen maken met de apotheek zouden in het bijzonder nuttig kunnen zijn, omdat adolescenten niet vaak naar de apotheek gaan, terwijl apothekers advies kunnen geven over het medicatiegebruik.

Het doel van dit proefschrift was om het perspectief van adolescenten op hun geneesmiddelgebruik in kaart te brengen, en om te onderzoeken wat het effect van een mHealth interventie (gekoppeld aan de apotheek) is op de therapietrouw en zelfmanagement van adolescenten met een chronische ziekte.

MEDICATIEGEBRUIK DOOR ADOLESCENTEN

In ***hoofdstuk 2*** onderzochten we het medicatiegebruik van adolescenten (N=79,398) door middel van apotheek aflevergegevens. Meer dan de helft van de ingeschreven adolescenten (59.7%; N=47,421) haalde een recept op. De helft van deze adolescenten haalden een recept op voor dermatologica (49.3%), gevolgd door medicatie voor het ademhalingsstelsel (41.8%), en antimicrobiële middelen voor systemisch gebruik (35.3%). Het percentage vrouwen dat tenminste één recept ophaalde was significant hoger dan het percentage mannen, voor bijna alle geneesmiddelgroepen, behalve voor medicatie voor het ademhalingsstelsel, zenuwstelsel, zintuigelijke organen, en systemische hormoonpreparaten, exclusief geslachtshormonen. Tijdens adolescentie nam het percentage mannen die dermatologica gebruikten toe, terwijl het percentage vrouwen verminderde met de leeftijd ($p<0.001$). De meeste recepten werden opgehaald voor medicatie voor het zenuwstelsel, ademhalingsstelsel, en dermatologica. Methylfenidaat was het meest opgehaalde geneesmiddel.

PERSPECTIEF VAN ADOLESCENTEN OP HUN CHRONISCH GENEESMIDDELGEBRUIK

In ***hoofdstuk 3*** hebben we het perspectief van adolescenten onderzocht op hun chronisch geneesmiddelgebruik. We hebben ons gefocust op de meest voorkomende aandoening bij adolescenten, zoals beschreven ***hoofdstuk 2***: atopische dermatitis, attention-deficit/hyperactivity disorder (ADHD), en astma.

We hebben in ***hoofdstuk 3.1*** de ervaringen, voorkeuren, en overtuigingen van adolescenten met atopische dermatitis ten opzichte van hun behandeling onderzocht. Adolescenten (leeftijd 15.3 ± 2.1 jaar) in deze focusgroep studie waren tevreden met de werkzaamheid van de medicatie, maar ze gaven de voorkeur aan een sneller en meer blijvend effect. De meeste adolescenten hadden weinig contact met hun arts en ze waren niet volledig therapietrouw; ze ontwikkelden hun eigen manier om hun geneesmiddelen te gebruiken. Ze hadden daarnaast vaak onjuiste opvattingen over de werking van die geneesmiddelen. Een aantal praktische suggesties werd genoemd om het medicatiegebruik te verbeteren, zoals een snellere huidabsorptie, een andere (makkelijkere) verpakking, en vaste vervolgafspraken met de arts. Op basis van deze resultaten hebben we geconcludeerd dat zorgverleners extra aandacht moeten besteden aan adolescenten met atopische dermatitis om ze meer bewust te maken van het principe van de lokale behandeling met crèmes en zalven, en te zorgen dat ze deze middelen op de juiste manier gebruiken.

Het doel van ***hoofdstuk 3.2*** was om meer inzicht te krijgen in de houding van adolescenten met ADHD tegenover hun medicatie. We hebben een cross-sectioneel onderzoek uitgevoerd met 181 adolescenten (leeftijd 14.2 ± 1.7 jaar). Methylfenidaat was het meest gebruikte geneesmiddel (92.3%; n=167). De helft van de adolescenten (51.4%; n=93) had last van bijwerkingen, zoals een verminderde eetlust en slaapproblemen. De meeste adolescenten (82.9%; n=150) hadden een onverschillige houding tegenover hun ADHD medicatie (weinig noodzaak en weinig zorgen) en meer dan de helft van de adolescenten (61.3%; n=111) was niet-therapietrouw. Opmerkelijk genoeg vonden de meeste adolescenten dat zij hun ADHD goed onder controle hadden. Op basis van deze resultaten adviseerden wij een regelmatige begeleiding van het gebruik van ADHD geneesmiddelen bij adolescenten.

In ***hoofdstuk 3.3*** hebben we ons gefocust op adolescenten met astma. Het doel was om de associaties tussen ziekte perceptie, medicatie opvattingen, therapietrouw, ziekte controle, en kwaliteit van leven te onderzoeken. Gegevens van 243 adolescenten (leeftijd 15.1 ± 2.0 jaar) die meededen aan het ADolescent Adherence Patient Tool (ADAPT) onderzoek (***hoofdstuk 4***) waren beschikbaar voor dit cross-sectioneel onderzoek. Meer dan de helft van de adolescenten (62.1%; n=151) was niet-therapietrouw, 77.4% (n=188) had ongecontroleerd astma, 42.8% (n=104) vond hun astma medicatie noodzakelijk, en 95.5% (n=232) had weinig zorgen over hun astma medicatie. Er was een sterke correlatie tussen astma controle en kwaliteit van leven (r=0.74). Opvattingen over ziekte en therapietrouw waren gecorreleerd met astma controle en kwaliteit van leven, met

de sterkste associatie tussen 'identity' (beleving van de klachten) en kwaliteit van leven (r=-0.66). Opvattingen over de geneesmiddelen waren wel geassocieerd met therapietrouw (r=0.38), maar niet met controle van de ziekte. We vermoeden dat beter controle van de ziekte leidt tot een afname van de therapietrouw. We concludeerden dat het beïnvloeden van opvattingen over de ziekte en het belang van therapietrouw kan leiden tot een verbetering van ziekte controle en kwaliteit van leven.

MOBILE HEALTH INTERVENTIES VOOR ADOLESCENTEN MET ASTMA

In ***hoofdstuk 4*** hebben we een interactieve mHealth interventie voor adolescenten met astma onderzocht. We hebben de ADAPT interventie ontwikkeld op basis van de wensen en voorkeuren van adolescenten. De opzet van het ADAPT onderzoek staat beschreven in ***hoofdstuk 4.1***. De ADAPT interventie bestond uit een smartphone applicatie (app) voor patiënten. Deze app was gekoppeld aan een computer programma in de openbare apotheek. De app bevatte verschillende functies met als doel zelfmanagement en therapietrouw te verbeteren. Deze functies waren (1) een vragenlijst waarmee de klachten over de tijd gevolgd kunnen worden, (2) een medicatie alarm om de geneesmiddelen niet te vergeten, (3) korte filmpjes als voorlichting, (4) chat met andere deelnemers om het contact met lotgenoten te verbeteren, en (5) een chat met de apotheker om het contact tussen de adolescent en hun apotheker te verbeteren. Bovendien, (6) verschenen er elke twee weken een paar vragen over de therapietrouw in de app. De ADAPT interventie is geëvalueerd in een onderzoek met 66 openbare apotheken, waarbij de interventie groep zes maanden toegang had tot de interventie. Astma patiënten van 12 tot 18 jaar konden meedoen aan het onderzoek en de therapietrouw werd gemeten door middel van zelf-rapportage met de Medication Adherence Report Scale (MARS).

In totaal hebben 234 adolescenten (147 in de controle groep en 87 in de interventiegroep) deelname aan het onderzoek afgerond (***hoofdstuk 4.2***). De gemiddelde leeftijd was 15.1 ± 1.9 jaar. Er was geen effect van de interventie op de therapietrouw in de gehele groep (p=0.25), maar de interventie verbeterde de therapietrouw van adolescenten die niet-therapietrouw waren (n=76; interventie effect +2.12; p=0.04). Het interventie effect was groter in adolescenten die naast niet-therapietrouw, ook geen controle over hun astma symptomen hadden (n=74; interventie effect +2.52; p=0.02). Er was geen effect van de interventie op de astma controle of kwaliteit van leven. Op basis van deze resultaten lijkt het niet zinvol de ADAPT interventie aan iedere adolescent aan te bieden. Echter, adolescenten die niet-therapietrouw zijn en onvoldoende astma controle hebben, kunnen er mogelijk wel baat bij hebben.

In ***hoofdstuk 4.3*** hebben we onderzocht hoe adolescenten de ADAPT interventie gebruikten, door middel van een log bestand waarin het app gebruik veilig werd opgeslagen. Het bleek dat 86 adolescenten (leeftijd 15.0 ± 2.0 jaar) de ADAPT app gemiddeld 17 keer hebben gebruikt per

persoon (range 1 - 113). Gemiddeld werden er drie verschillende functies gebruikt, en 13% van de adolescenten (n=11) had alle functies van de app gebruikt. De meeste adolescenten gebruikten de vragenlijsten om de klachten en de therapietrouw te monitoren, daarna de filmpjes, de chat met de apotheker, en de chat met de andere deelnemers. Vrouwen gebruikten de app vaker dan mannen (p=0.01), en gedurende een langere periode (p=0.03). Het totale app gebruik had geen effect op de therapietrouw, maar het gebruik van de chat met de apotheker had wel een positief effect op de therapietrouw (p=0.01). Dit suggereert dat mHealth interventies voor adolescenten met astma meerdere functies moeten bevatten, en dat het 'chatten' met de zorgverlener verder gestimuleerd moet worden.

IMPLEMENTATIE VAN MHEALTH IN DE OPENBARE APOTHEEK

Hoofdstuk 5 gaat over de implementatie van mHealth interventies in de openbare apotheek. Proces evaluaties zijn belangrijk voor de implementatie. Daarom hebben we de ADAPT interventie geëvalueerd in ***hoofdstuk 5.1***. Apothekers (N=23) en patiënten (N=82) waren positief over de ADAPT interventie en ondervonden gunstige effecten. De meeste patiënten (78.0%; n=64) zouden de ADAPT interventie aanbevelen aan anderen. Daarnaast was de meerderheid (63.4%; n=52) het eens dat de apotheek de juiste plek is om informatie over de behandeling te ontvangen. De mogelijkheid om astma klachten te monitoren werd gewaardeerd door patiënten en apothekers. Bijna alle apothekers (95.7%; n=22) waren tevreden over ADAPT, en het gebruik van de interventie kostte niet veel tijd (91.3%; n=21). De ADAPT interventie verbeterde het contact met de patiënten (73.9%; n=17) en bevorderde de zorgverlenende rol van apothekers (82.6%; n=19). Apothekers die niet met de ADAPT interventie gewerkt hebben, noemden 'tijd' en 'financiering' als belangrijkste belemmeringen voor het gebruik van mHealth. Deze evaluatie studie laat zien dat er mogelijkheden zijn om de kwaliteit van de zorg te verbeteren met behulp van mHealth en het benadrukt de noodzaak voor verdere implementatie van mHealth in de klinische praktijk.

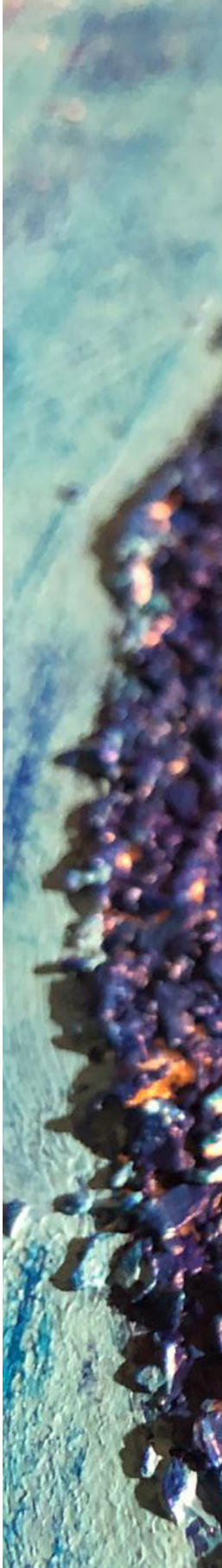
Het proces om een nieuwe interventie onderdeel te laten worden van de dagelijkse routine (dat het vanzelfsprekend wordt) is een complex en continu proces. Dit wordt ook wel normalisatie genoemd. In ***hoofdstuk 5.2*** hebben we door middel van de Normalization Process Theory (NPT) de normalisatie mogelijkheden onderzocht van de ADAPT interventie. NPT is een sociologische actietheorie, waarmee factoren verklaard kunnen worden die de implementatie, inbedding, en integratie van nieuwe interventies in de klinische praktijk bevorderen of belemmeren. Apothekers begrepen het doel van de ADAPT interventie en waren bereid om de noodzakelijke handelingen uit te voeren zodat de interventie in de praktijk gebruikt kan worden. Echter de tijd die nodig is om de interventie te gebruiken, was een belangrijke belemmering in de afwezigheid van een passende vergoedingsregeling. Om de normalisatie te verbeteren zijn er apothekers nodig die het voortouw nemen. Daarnaast zijn passende vergoedingsregelingen belangrijk, zodat men er zeker van kan zijn dat apothekers (blijven) meedoen. De normalisatie wordt ook verbeterd door

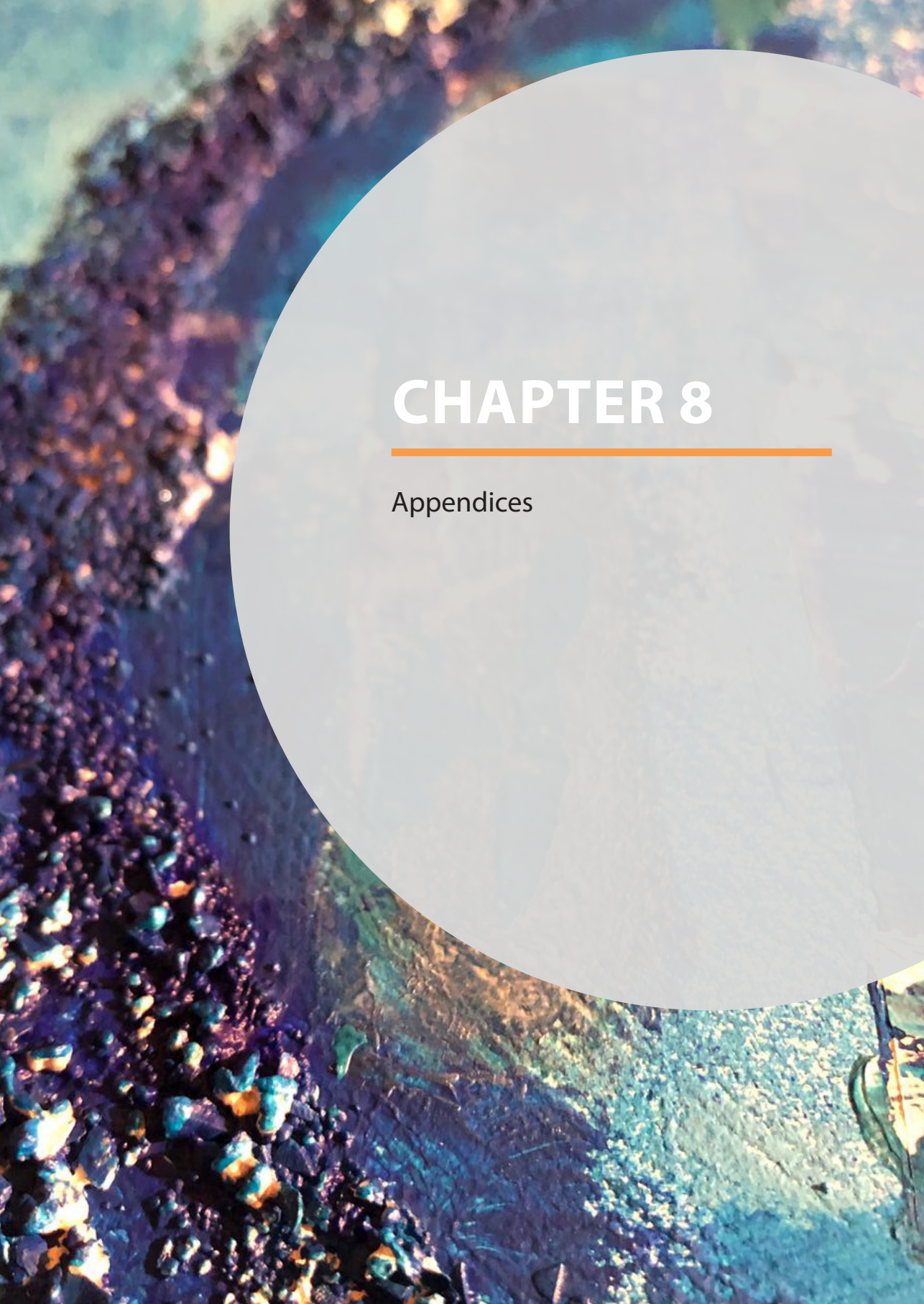
de steun van beroepsorganisaties. Derhalve is er een mogelijkheid om de ADAPT interventie te normaliseren in de openbare apotheek, echter zijn er veranderingen nodig in de klinische praktijk en vergoedingsregelingen.

ALGEMENE DISCUSSIE

In ***hoofdstuk 6*** hebben we de belangrijkste resultaten samengevat en zijn we verder ingegaan op adolescenten in de gezondheidszorg en op het perspectief van adolescenten over hun chronisch geneesmiddelgebruik. We hebben het therapietrouw probleem en interventie mogelijkheden, waaronder de ADAPT interventie, verder besproken. Daarnaast hebben we de resultaten in een breder perspectief geplaatst en hebben we de mogelijkheden voor mHealth in de apotheek (en daarbuiten) besproken. We hebben tevens verschillende aspecten van mHealth uitgelicht, waaronder de kosteneffectiviteit. Tot slot hebben we aanbevelingen gedaan voor effectief gebruik, en de verdere implementatie van mHealth. Ook hebben we een aantal richtingen voor verder onderzoek behandeld.

We concludeerden dat adolescenten met chronische aandoeningen een speciale patiënten groep zijn, die extra aandacht nodig hebben van zorgverleners. Een persoonlijke en aangepaste benadering is gesuggereerd, want adolescenten hebben unieke behoeften en wensen, en ze zijn vaak minder therapietrouw. Een aangepaste mHealth interventie met verschillende functies kan nuttig zijn, met name als er een mogelijkheid is om de klachten te monitoren en er een mogelijkheid is om te chatten met zorgverleners. Voor de verdere implementatie van mHealth in de apotheek (of in de gezondheidszorg in het algemeen) is het van groot belang dat mHealth routinematig gebruik gaat worden in de dagelijkse klinische praktijk.





CHAPTER 8

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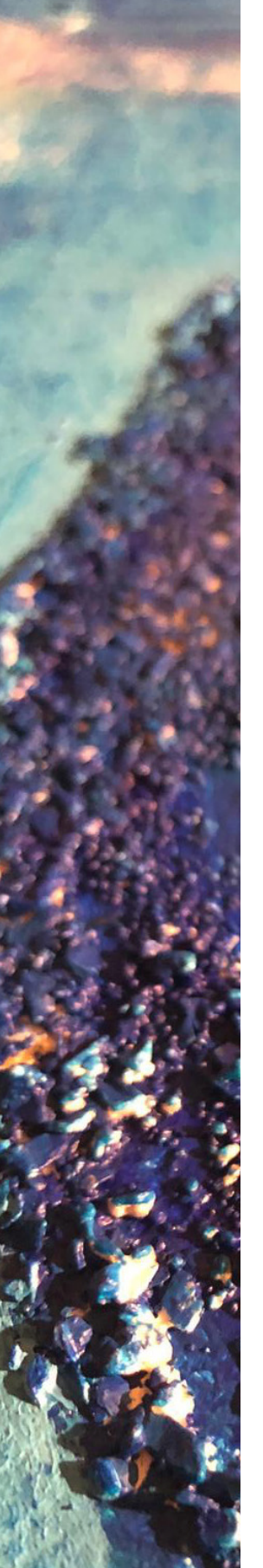
Dankwoord



De afgelopen vier jaar heb ik met veel plezier onderzoek gedaan bij de afdeling Farmaco-epidemiologie en Klinische Farmacologie. Ik ben dankbaar dat ik de kans heb gekregen om mijn promotieonderzoek hier te doen. Graag wil ik via deze weg iedereen bedanken die een bijdrage heeft geleverd aan mijn onderzoek (en de leuke tijd) in de afgelopen jaren. Hierbij maak ik ook graag van de gelegenheid gebruik om een paar mensen in het bijzonder te bedanken.

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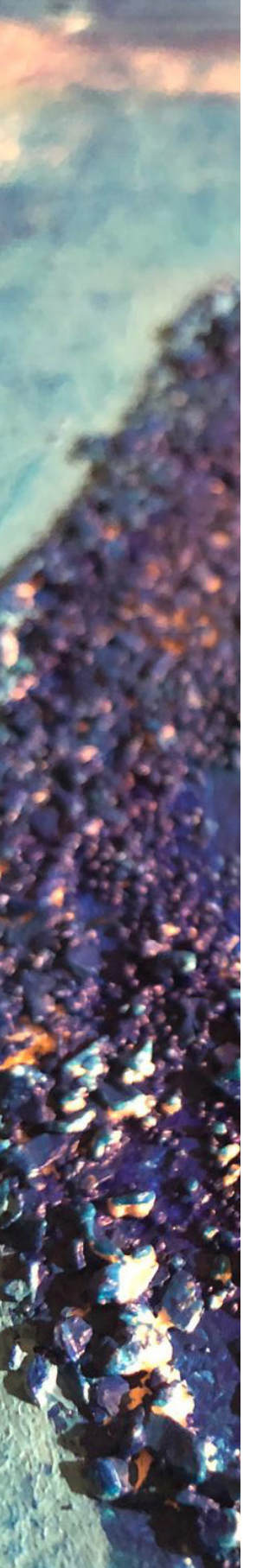
CHAPTER 8

List of co-authors



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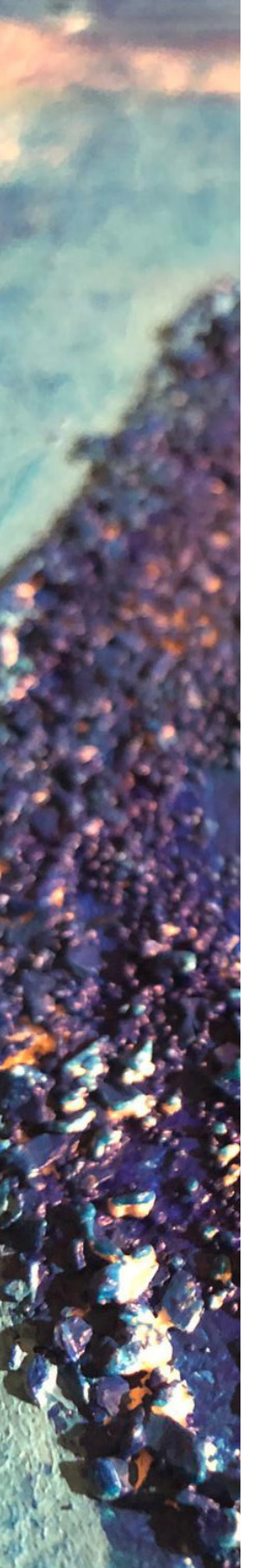
List of publications



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Kosse RC, Bouvy ML, Belitser SV, de Vries TW, van der Wal PS, Koster ES. Effective engagement of adolescent asthma patients with mHealth supporting medication adherence. *JMIR Mhealth Uhealth* 2019 [accepted for publication].
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(INTER)NATIONAL ABSTRACTS RELATED TO THIS THESIS

Implementation of an asthma adherence mHealth intervention in the community pharmacy setting: a sociological approach. *22nd ESPACOMP conference*, 29 November - 1 December 2018, Dublin, Ireland. [oral presentation]

The ADAPT mHealth intervention increases inhaled corticosteroid adherence in adolescents with asthma. *22nd ESPACOMP conference*, 29 November - 1 December 2018, Dublin, Ireland. [poster presentation; runner-up poster prize]

Mobile health intervention increases inhaled corticosteroid adherence in adolescents with asthma. *34th ICPE Conference*, 22 - 26 August 2018, Prague, Czech Republic. [spotlight poster presentation; spotlight poster winner]

Mobile health intervention increases adherence in adolescents with asthma: a cluster randomised controlled trial in community pharmacies. *1st FIP conference*, 25 - 27 June 2018, Lisbon, Portugal. [oral presentation]

Mobile health intervention to support self-management: pharmacists' and patients' perceptions. *1st FIP conference*, 25 - 27 June 2018, Lisbon, Portugal. [poster presentation]

Smartphone app verbetert de therapietrouw van adolescenten met astma. *39th NVK conference*, 13 - 15 June 2018, Arnhem, The Netherlands. [SLAM presentation]

Mobile health interventie verbetert therapietrouw van adolescenten met astma: resultaten van de ADAPT studie. *PRISMA symposium*, 15 May 2018, Amersfoort, The Netherlands. [oral presentation]

Asthma mHealth intervention increases adherence in adolescent with poor adherence rates. *7th ARPH conference*, 25 - 26 January 2018, Tilburg, The Netherlands. [oral presentation; best oral presentation award]

Changing patterns of drug utilization: from childhood to adulthood. *33rd ICPE Conference*, 26-30 August 2017, Montréal, Canada. [poster presentation]

Implementatie van een mobile health interventie in de apotheek: het apothekersperspectief. *PRISMA symposium,* 16 May 2017, Amersfoort, The Netherlands. [oral presentation]

Development and testing of an ADolescent Adherence Patient Tool: interim analysis of the ADAPT study. *6th ARPH conference*, 2 - 3 February 2017, Leiden, The Netherlands. [poster presentation]

ADHD medication use by adolescents; adherence, attitudes and beliefs. *PRISMA symposium*, 24 May 2016, Amersfoort, The Netherlands. [oral presentation]

The ADAPT intervention: interactive mHealth application for adolescent asthma patients to improve medication intake behaviour. *5th ARPH conference*, 28 - 29 January 2016, Maastricht, The Netherlands. [eHealth demonstration]

Astma app: een oplossing voor het verbeteren van therapietrouw bij jongeren? *PRISMA symposium,* 19 May 2015, Amersfoort, The Netherlands. [oral presentation]