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Nationwide use of theophylline among adults
- A 20-year Danish drug utilisation study

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Running head: Theophylline utilisation
DPH, JRD, CBL declare no conflicts of interest
Abstract
Background
Theophylline, a dimethylxanthine, has been used the last 100 years to treat airway disease. Although it is one of the most widely prescribed medicines to treat asthma and chronic obstructive pulmonary disease (COPD) throughout the years, the utilisation patterns are not well-described.

Methods
Using the Danish Register of Medicinal Products Statistics, we identified adults above 18 years redeeming one or more prescriptions of theophylline between 1997 up to 2017, with a 2-year run-in period from 1995 to 1997. Using descriptive statistics, we reported the development in prevalence, incidence, and a measure of treatment duration (proportion of patients covered).

Results
In total, 55,636 individuals redeemed 1,066,475 prescriptions of theophylline, 30,619 women (55%) and 25,017 men (45%). The prevalence decreased from 401 per 100,000 individuals in 1997 to 26 per 100,000 individuals in 2016. The incidence rate decreased throughout the entire study period (105 per 100,000 person-years in 1997 to 5 per 100,000 person-years in 2016). The proportion of patients was 52% after three months after initiation, 33%, 27%, and 23% were current users after 6 months, one year, and two years.

Conclusions
Although newer and more efficient medicines to treat asthma and COPD has been developed, theophylline is still prescribed and used in 2016, but the incidence and prevalence have decreased markedly since 1997.

Highlights
•
Introduction

Theophylline, a dimethylxanthine, is considered one of the most widely prescribed drugs to treat obstructive pulmonary diseases [1]. The structure is very related to caffeine [2], and theophylline occurs in coffee beans, cocoa beans and tea, although only in trace amounts. Henry Hyde Salter, MD, FRCP, wrote in his report from 1859, that "One of the commonest and best-reputed remedies of asthma, one that is almost sure to have been tried in any case that may come under our observation, and one that in many cases is more efficacious than any other, is strong coffee" [3]. As a medical drug, theophylline was initially extracted from tea leaves and synthesised in 1895 as a diuretic [1].

The mechanism of action is not established, but is believed to include phosphodiesterase inhibition, adenosine receptor antagonism, as well as increased interleukin-10 concentrations [1,4]. The drug has two primary pharmacodynamic actions dependent on the plasma concentrations (bronchodilation and antiinflammation). It was initially used as a bronchodilator, but in order to achieve significant bronchodilatation relatively high plasma concentrations are needed (10–20 mg/l) [1,5,6]. Along with introduction of new direct bronchodilators, the drug is now considered inferior for bronchodilation in asthma and COPD treatment due to a weak efficacy combined with common side-effects and risk of toxicity at higher doses [7].

However, in lower concentrations, theophylline is considered to have anti-inflammatory effects, which have been a subject of interest in research the recent years, especially in regards to COPD patients with glucocorticoid resistance [5,8]. Therefore, it is likely that the patient population who receives treatment with theophylline is different now from those who initiated treatment 20 years ago.

Although theophylline has been on the market for almost a century, and significant changes in treatment guidelines of obstructive pulmonary diseases has occurred, very little is known about its utilisation pattern in a population. The few studies available are primarily questionnaire surveys [9,10], or performed on selected patient populations [11,12].

In such, we aimed to describe theophylline use among adults in Denmark since 1997, using drug utilisation statistics developed for individual-level prescription data [13].
Methods
In this nationwide utilisation study, we described the outpatient use of theophylline including assessment of duration during 1 January 1997 to 31 December 2016 among all adult Danish inhabitants.

Setting

Data Sources
Three Danish nationwide registers were used to assess and identify individuals redeeming prescriptions of theophylline: Danish Civil Registration System [14], The Register of Medicinal Products Statistics [15], and The Danish National Patient Register [16]. The Danish National Health Service provides tax-supported health care for the entire Danish population, and due to the unique personal identification number assigned to all Danish citizens it is possible to conduct true population-based register-linkage studies covering the entire population [14].

Study drugs
The DDD for theophylline (ATC R03DA04) is 400 mg, according to the WHO Collaborating Centre for Drug Statistics Methodology ATC/DDD index [17]. The approved therapeutic indication includes asthma bronchiale and other bronchospasms. The marketed formulations are oral sustained release tablets [18].

Each individual was considered as a ‘current user’ on a given day if they had a recording of a redeemed theophylline prescription with enough doses to cover that day. The duration of each prescription was defined as the number of DDDs dispensed (i.e., assuming a consumption of one DDD per day), while adding 25% to the duration to account for secondary non-compliance or irregular prescription patterns. The addition of 25% to the duration of therapy is based on a definition of 80% compliance, which previously has been used as an arbitrary cut-off [19–21]. We excluded individuals less than 18 years of age and computed a run-in period of two years (1995-1997), in order to decrease the risk of misclassifying new users.

Analysis
Users were defined as individuals redeeming one or more prescriptions of theophylline in a given year. We calculated the amount of DDD redeemed per individual for each year within the study period.

We calculated the total number of users of theophylline per year and the total annual amount of DDDs filled within the same period, to describe the amount of theophylline used per individual each year.
The number of current users per 1,000 in the population, from 1997 up to 2017 was calculated (the point prevalence proportions) using the total population living in Denmark 1 January of each relevant year. The gender and age-specific (1-year intervals) prevalence proportion for 2016 was reported.

We used the ‘proportion of patients covered’ (PPC) method as an estimation of treatment duration [22]. We followed all users from the date of their first prescription of theophylline. Over time, we estimated the proportion of all individuals still alive after X days, who seemingly still used theophylline at that day (defining current use as in the analysis of point prevalence). Thereby, an individual could be regarded as dropped out of treatment at one point in time and later be re-classified as current user upon filling a new prescription. We divided the analysis into the age groups: 0-18, 19-39, 40-64, and 65-90+ year old. Subgroup analyses included gender, and calendar year of first prescription.

Lastly, we computed Lorenz curves to assess the proportion of theophylline use that was accounted for by percentiles of theophylline users, ranked according to their annual consumption.

Stata Version 14.1 (StataCorp, College Station, TX, USA) was used for all analyses.

Ethics
The study was approved by the Danish Data Protection Agency. According to Danish law, register-based studies do not require approval from an ethics review board [23].

Results
Demographics
In total, 55,636 individuals redeemed 1,066,475 prescriptions of theophylline. A total of 15,934 (29%) individuals redeemed only one theophylline prescription, 9,286 (17%) redeemed 2-4 prescriptions, and 32,304 (58%) redeemed 5+ prescriptions. The median number of DDDs filled per prescription was 75 (Inter Quartile Range [IQR] 63-75).

The median age of individuals initiating theophylline was 69 years (IQR 58-76 years), with a majority of female users (n=78,760, 55%), who initiated theophylline at a younger age than males (female median age 68 years [IQR 57-76 years], male median age 70 years [IQR 60-77 years], p<0.001). In total, 2.7% (n=1,491) had an asthma-related admission up to a year prior to theophylline initiation, whereas 13.1% (n=7,282) had a COPD-related admission.

Incident users in 1997-2006 versus 2007-2016
In total, 49.1% the patients who initiated theophylline in 1997-2006 redeemed a prescription of inhaled corticosteroid (ICS), decreasing to 20.3% among new users in 2007-2016. The opposite trend was
observed in fixed-dose long acting beta-2-agonists (LABA) in combination with ICS. Among patients who initiated theophylline in 1997-2006 2.0% had redeemed a prescription of long-acting muscarinergic agonists (LAMA) prior to the theophylline initiation, whereas 44% redeemed a prescription of LAMA patients initiating theophylline in 2007-2016. The COPD-related admissions increased from 12.2% among incident users in 1997-2006 to 23.1% among incident users in 2007-2016.

The demographic characteristics of individuals initiating theophylline are presented in Table 1.

Prevalence, incidence, and amount used
The total amount of DDDs was 10,227,000 in 1997, and 668,000 in 2016. For trends in amounts used, please refer to Figure 1.

The number of theophylline users in treatment each year decreased during the study period, from 401 per 100,000 individuals in 1997 to 26 per 100,000 individuals in 2016 (Figure 2). The age-specific point prevalence showed a majority of older users in the four years we have presented (Figure 3).

The number of incident users decreased from 105 per 100,000 person-years in 1997 to 5 per 100,000 person-years in 2016. A small spike in incidence rates in 2006 is observed. The most pronounced decrease in incidence rates is observed among individuals in the age-group 65+ years (from 377 per 100,000 in 1997 to 13 per 100,000 in 2016) (Figure 4).

Duration of usage
Overall, 52% were current users of theophylline three months after initiation, 33%, 27%, and 23% were current users after 6 months, one year, and two years, respectively (Figure 5). The lowest proportion still treated after two years was among the age-group 18-39 years (7%), whereas 28% of users aged 70-79 years were still treated one year after their first filled prescription.

Lorenz-curves
Lorenz curve of theophylline use in the period 1997-2006, and 2007-2016 are shown in Figure 6. In the former period 50% of users represented 95.2% of the sold amount of theophylline DDDs, whereas in the latter period 50% of users represented 94.4% of the sold amount.
Discussion

This is the first study to report the utilisation patterns of theophylline among adults in a nationwide population over 20 years. We found, as suspected, a decrease of theophylline use in the study period. The decrease was observed both in new users (incidence) but also in current users (prevalence). We found that less than one fourth of all who initiated theophylline were current users after two years.

Different studies have assessed the utilisation of theophylline. In a large retrospective study based on administrative data from the Kaiser Permanente healthcare plan among patients with a diagnosis of asthma, 0.6% were treated solely with theophylline, whereas 0.8% were treated with a combination of inhaled corticosteroids (ICS), and 0.4% in a combination of long-acting-beta-agonists (LABA), ICS, and theophylline [12]. A questionnaire-based survey was conducted among 200 asthma patients in Sweden and Brazil showed that Brazilian patients were more likely to be using theophylline than patients in Sweden (18% vs 1%). A Taiwanese study analysing nationwide administrative data showed a difference in prescription patterns of anti-asthmatic medicines according to the speciality of physician who prescribed the medicines [11]. Unfortunately, we were not able to identify the individual physician or which speciality the drug was from.

However, a common tendency in these studies was that they identified asthma or COPD patients initially and then assessed the utilisation patterns, which potentially introduce misclassification of the utilisation patterns due to the variable validity of the identification methods used [24–26].

We found that the demographic characteristics of patients initiating theophylline was different among patients initiating the treatment in the period 1997-2006 compared to those, who initiated treatment in 2007-2016. Almost half the patients who initiated theophylline in 1997-2006 redeemed a prescription of ICS whereas only a fifth of all patients initiating theophylline in the later period redeemed an ICS prescription.

The opposite trend is observed in LABA+ICS fixed dose combination, where an increase from 3.75 to 57.4% was observed. This could indicate, that the asthma guidelines are followed, but also reflect theophylline use as an indicator of disease severity in especially asthma patients (i.e. confounding by indication). This theory is strengthened by the observation, that treatment with oral steroids up to a year prior to theophylline initiation increased from 34.7% in the period 1997-2006 to 48.7% in the period 2007-2016. Also, the asthma-related admissions up to a year prior to theophylline-initiation increased from 2.5% to 4.6%, which also strengthen our theory.

However, we observed a two-times increase in the prior COPD-related admissions in the latter period.
compared to the former (12.2% to 23.1%). This could indicate, that theophylline-initiation is increasingly shifting indication from asthma to COPD.

Notably, we found that only 2% of all patients who initiated theophylline in 1997-2006 had redeemed a prescription of LAMA prior to the theophylline initiation, whereas this percentage increased to 44% among patients initiating theophylline in 2007-2016. This might be explained three scenarios: 1) that treatment with theophylline has shifted from patients with asthma to patients with COPD, 2) as an indicator of confounding of severity in asthma patients due to the introduction of LAMA for obstructive and severe asthma in GINA guidelines in the latter period or 3) a general tendency of an increasing usage of LAMA. This is in accordance with the recent research where theophylline has been used as an anti-inflammatory supplementary treatment in COPD patients with ICS resistance [5,8]. Furthermore, the introduction and popularity of other oral supplementary treatments like montelukast might have had a negative impact of the theophylline usage, because of the similar indications [7,21].

Indeed, the overall proportion of all Danish adults redeeming prescriptions of inhaled bronchodilators and/or ICS has increased from 2.6% in 2000 to 4.5% by the end of 2016 [27]. The most pronounced increase in point prevalence proportion among the adult general population was observed in fixed dose LABA and ICS, from 0.1% in 2000 to 1.8% in 2016. Furthermore, the point prevalence proportion of patients treated with LAMA in the general population has also increased significantly from 2003 to 2016 [27].

Our study has several strengths. The nationwide setting allows the analysis of theophylline utilisation in the entire Danish population regardless of gender, race, age, insurance status, or household income. The unbiased data collection from all outpatient public pharmacies, which the Danish Register of Medicinal Products Statistics consists of, allowed our analysis to be conducted over a 20-year period with no risk of dropout [15].

However, some limitations exist. The most important limitation is, that the Register of Medical Products Statistics does not contain information on the prescribed daily dose. Therefore, we had to use the number of redeemed DDDs adding 25% to the duration of therapy is based on a definition of 80% compliance. We defined one daily dosing as one DDD, which is 400 mg, according to the WHO [17]. According to summary of product characteristics (SmPC) the usual maintenance dose of theophylline is 200 mg 12 hourly among adults and elderly. However, depending on the therapeutic response, it may be titrated to either 300 mg or 400 mg [28]. This could impact both the prevalence estimations, as well as the PPC analysis. However, we do not believe, that did have an influence on the estimations. The PPC analysis provides for this particular problem.
The aim of the current study was to describe theophylline usage over time, and thus several questions remain for future studies. It would be interesting to address the indications of theophylline prescriptions, and to analyze the possible shift over time. The treatment indications are not listed in the Register of Medicinal Products Statistics and data could thus not be supplemented with clinical journal data. In such, the current study’s conclusion is thus based on surrogate markers of treatment indications.

Conclusions

Although newer and more efficient medicines to treat asthma and COPD has been developed, theophylline is still prescribed and used in 2016, but the incidence and prevalence have decreased markedly since 1997 in line with guideline recommendations for obstructive airway diseases. The characteristics of patients who initiated theophylline have changed since 1997, presumably towards supplementary treatment of patients with COPD or as ‘last choice’ treatment in uncontrolled asthmatics with severe disease.

Acknowledgements

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References


17. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and


<table>
<thead>
<tr>
<th>Table 1: Baseline characteristics of patients initiating theophylline</th>
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<tbody>
<tr>
<td><strong>Total</strong> (n=55,636)</td>
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<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Age, median (IQR)</td>
</tr>
<tr>
<td>Sex</td>
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<tr>
<td>Female</td>
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<tr>
<td>Male</td>
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<tr>
<td>Charlson Comorbidity Index (CCI)</td>
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<tr>
<td>0</td>
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<tr>
<td>1</td>
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<tr>
<td>2</td>
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<tr>
<td>&gt;= 3</td>
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<tr>
<td>Admissions*</td>
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<tr>
<td>Asthma-related</td>
</tr>
<tr>
<td>COPD-related</td>
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<tr>
<td>Both asthma- and COPD related diagnosis</td>
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<tr>
<td>Chronic respiratory failure</td>
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<tr>
<td>Concurrent medication* §</td>
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<tr>
<td>SABA $</td>
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<td>ICS</td>
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<td>LABA+ICS</td>
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<td>Montelukast</td>
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<td>Oral steroids</td>
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IQR inter-quartile range; CCI Charlson comorbidity index; COPD chronic obstructive pulmonary disease; SABA short-acting beta-2-agonists; SAMA short-acting muscarinic agonists; LABA long-acting beta-2-agonists; LAMA long-acting muscarinic agonists; ICS inhaled corticosteroids

* Up to a year prior to initial theophylline prescription

§ Percentages may add to more than 100%, as a patient may be counted in more than one category

$ Including SABA+SAMA combination
Figure legends

**Figure 1:** Total amount of dispensed DDD, specified by sex and year in Denmark from 1997 to 2016

**Figure 2:** Overall point prevalence proportion of theophylline use in Denmark from 1997 to 2016

**Figure 3:** Age and sex-specific prevalence proportions of theophylline by end of 2016

**Figure 4:** Standardised incidence rates of theophylline from 1997 to 2016

**Figure 5:** Duration of theophylline therapy

**Figure 6:** Lorenz-curves for theophylline use in the periods 1997-2006, and 2007-2016. The graph shows the proportion of theophylline use that is accounted for by percentiles of theophylline users, ranked according to their annual theophylline consumption. The dashed line represents 50-percentile of users.
Total drug use (million DDDs)

Year

Total
Female
Male
Point prevalence proportion per 100,000 inhabitants

Years
2016

Prevalence proportion per 1000 inhabitants

Males

Females

Age

0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90

0 0.5 1 1.5 2

Prevalence proportion per 1000 inhabitants
Incidence rate (per 100,000 person-years)

Years


Total
65+ years
40-64 years
18-39 years

Total
65+ years
40-64 years
18-39 years
Highlights

- Theophylline has been used the last 100 years to treat airway disease
- Usage has decreased markedly since the introduction of newer inhaled bronchodilators
- Only one in four are still in treatment after one year
- Patients who initiate theophylline to patients more likely to have COPD than asthma now, than 10-20 years ago