ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

The Ontario Drug Policy Research Network Drug Class Review on Combination Inhaled Corticosteroids and Long Acting Beta Agonists (ICS/LABA) for the Treatment of Chronic Obstructive Pulmonary Disease (COPD)

Final Report of Qualitative Study Results

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Executive Summary

Background: The Ontario Drug Policy Research Network (ODPRN) conducted a drug class review of combination inhaled corticosteroids and long-acting beta agonists (ICS/LABA) for the treatment of chronic obstructive pulmonary disease (COPD), which was selected as part of a formulary modernization initiative by the Ontario Public Drug Programs. This report highlights the findings of the qualitative study performed within the drug class review to determine the experiences of managing or treating COPD with ICS/LABA.

Methods: We used qualitative methods in a framework approach. One-on-one telephone interviews were conducted with 25 patients and caregivers, 7 physicians (i.e., primary care physicians and respirologists), and 6 pharmacists. Interviews were recorded and analyzed using a framework for pharmaceutical policy analysis (i.e., the "Triple-A" framework: affordability, appropriateness, and accessibility of medications). Emergent findings were integrated into our framework, and the framework was adapted to convey specific experiences and perceptions relevant to ICS/LABA funding policies.

Key Findings: Findings in this report are summarized to represent common experiences and perceptions described across patient, physician, and pharmacist groups.

COPD is perceived to affect overall quality of life: Patients with COPD may experience symptoms, such as shortness of breath, coughing, and excessive mucous production. Many participants noted a significant decline over time in their ability to engage in physical activity. They expressed, however, that they are attempting to remain active by making adjustments to the type and pace of activities performed so that they can relieve symptoms but also maintain normalcy.

Participants differed in their perceptions of the effectiveness of ICS/LABA products in comparison to that of other COPD drugs and to no treatment: they perceived COPD therapies, such as ICS/LABA, to be useful for preventing exacerbations, but they had mixed views on the effect of ICS/LABA on quality of life. Specifically, clinician participants expressed that these maintenance drugs should be reserved for patients with severe COPD even though clinical guidelines indicate that these drugs can be used for moderate-to-severe COPD. Participants from all groups found it challenging to comment on the effectiveness of this group of drugs specifically because many patients take these drugs in conjunction with other products, such as long-acting muscarinic antagonists (long-acting anticholinergics or LAMAs). There are also challenges with the overdiagnosis and underdiagnosis of COPD that can affect both the appropriateness of treatment and access to appropriate medications.

Accessing ICS/LABA is not difficult for most individuals: Participants indicated that the majority of COPD patients are individuals over the age of 65 years. ICS/LABA is frequently prescribed to these ODB-eligible patients even though there is no listing on the formulary for COPD indications. Physicians may resort to using the Limited Use (LU) code 330 to access these drugs for their patients. Many patients receive ICS/LABA products early in their COPD diagnosis even though both physicians and pharmacists have reservations about the appropriateness of the prescription and

the benefits of the drug class itself. Patients under 65 years of age who do not have coverage are at a great disadvantage and are often unable to afford COPD therapies.

Conclusion: The findings from the qualitative study of the ICS/LABA drug class review informed the methods of other ODPRN research units that are conducting studies for the review. They also helped to contextualize the review's results. Overall, our findings shed light on the experiences of prescribing, dispensing, and using ICS/LABA for COPD treatment and unveil important information that can affect how patients access these drugs across Ontario.

Part 1: Introduction and Background

The Ontario Drug Policy Research Network (ODPRN) recently received funding to conduct a series of drug class reviews as part of an initiative to update the public drug formulary (i.e., formulary modernization). As such, the ODPRN works closely with the Ontario Public Drug Programs (OPDP) at the Ministry of Health and Long-Term Care (MOHLTC) to select key priority areas and topics for formulary modernization, conduct independent drug class reviews, and disseminate the results of the reviews to the OPDP to facilitate informed decision making on public drug funding policies. Combination inhaled corticosteroids and long-acting beta agonists (ICS/LABA) for the treatment of chronic obstructive pulmonary disease (COPD) was selected as the topic for the second drug class review.

ICS/LABA is one of multiple groups of drugs used for treating COPD. According to the Canadian Thoracic Society guidelines, ICS/LABA should be prescribed to patients with moderate-to-severe COPD if exacerbations of COPD symptoms do not improve or worsen despite appropriate treatment (O'Donnell et al., 2007). Symptoms can be alleviated by ICS/LABA combination products through the anti-inflammatory action of the ICS component and the bronchodilation action of the LABA component. In comparison to short-acting products (e.g., salbutamol and ipratropium), ICS/LABA combination products are meant to prevent exacerbations over the long term.

Currently, there is limited information on how physicians decide to prescribe ICS/LABA and how patients decide to adhere to their prescribed treatment. Moreover, since ICS/LABA is recommended as part of COPD treatment but is not listed in the Ontario Drug Benefit (ODB) for COPD indication, it is unclear how patients are accessing this group of drugs. A large proportion of patients with COPD are eligible to obtain drugs through the ODB (i.e., patients over 65 years of age). At this time, however, ICS/LABA is listed under a Limited Use code (restricted access) for asthma indications only.

The purpose of the qualitative study component of the ODPRN drug class review on ICS/LABA is to explore the factors that may be related to prescribing, dispensing, and using ICS/LABA to treat moderate-to-severe COPD. This information is important for understanding and contextualizing prescription and usage patterns in Ontario and for highlighting health equity issues that may be prevalent but currently unknown. The findings from the qualitative study were also used to inform

the research plans of the other drug class review research units to ensure that stakeholder issues and priorities were being considered in their analyses.

Part 2: Methods

Design

We used a framework approach to qualitative research (Ritchie & Spencer, 1994). This approach helps researchers focus on specific areas of interest when exploring a topic using qualitative methods, which can make the findings more applicable than when alternative qualitative procedures are used. However, the approach also maintains the flexibility of qualitative methods to incorporate new ideas, emergent issues, or unanticipated results. The framework selected for this study was the "Triple-A" framework (see **Appendix A**) for pharmaceutical policy analysis developed by Morgan et al. (2009). This framework highlights the need to explore affordability, accessibility, and appropriateness of drugs when determining policy-relevant issues.

Sampling

Stakeholders identified to take part in the ICS/LABA drug class review included physicians (i.e., primary care physicians [PCPs] and respirologists) and pharmacists who have prescribed or dispensed ICS/LABA and patients with COPD who have current or prior experience using ICS/LABA. We also recruited caregivers of patients if the patients themselves were unable to participate in the interview. We aimed to recruit 6 to 8 physicians, 6 to 8 pharmacists, and 20 to 25 patients based on the assumption that these sample sizes would be sufficient to reach saturation of findings among relatively homogenous groups of participants (Kuzel, 1999). Participants were recruited from across Ontario.

We aimed to recruit physicians working at large academic centres and community clinics; community pharmacists; and patients with a range of experiences, backgrounds, and self-reported levels of disease severity. Geographic variation was considered in the recruitment process.

A purposive sampling approach using a convenience sample was used to recruit participants who will be involved in or affected by drug policy decisions related to ICS/LABA. Recruitment methods included a) cold calling; b) e-mailing and faxing; c) recruiting at primary care and specialist clinics; d) sending recruitment letters through e-mail distribution lists of professional organizations and advocacy groups; e) posting recruitment notices to the ODPRN website and social media accounts (i.e., Twitter and Facebook); and g) snowball sampling (i.e., asking participants to connect with individuals they know for the purpose of recruitment to the study).

Data Collection and Analysis

Qualitative data were collected through one-on-one, telephone interviews that were 30 to 45 minutes long and conducted between November 2013 and January 2014. All interviews were conducted with a semi-structured interview guide that was developed using the "Triple-A" framework for pharmaceutical policy analysis (Morgan et. al., 2009) and input from clinicians and the drug class review team. Each interview was audio recorded and transcribed. The interview

transcripts comprised the primary source of data. The interviewer and/or a note taker took field notes during the interview to serve as a secondary source of data.

The framework approach was used to guide data analysis. Two independent analysts engaged in familiarization of the data by reading all primary and secondary data sources and generating initial codes that could be incorporated into the "Triple-A" framework (Morgan et. al., 2009). These codes comprised the coding framework, which was reviewed by the qualitative research team and then applied to the data by two analysts during in-depth analysis. Inter-rater reliability between the two analysts was > 80%. The analysts and the qualitative research team mapped and interpreted the coded data to generate the final themes.

Research Ethics

This study was approved by the St. Michael's Hospital Research Ethics Board in Toronto, Ontario, Canada in November 2013.

Part 3: Findings

Participant Demographics

Patients and caregivers

A total of 24 patients and one caregiver who spoke on behalf of a patient participated in the study. (Patients and caregivers will hereon be referred to as patients.) Of these patients, 13 (52%) were male and 12 (48%) were female. The majority of participants (n = 18; 72%) were over the age of 65 years. There was one participant between the ages of 45 and 54 years and six participants between the ages of 55 and 64 years. Patient participants had a variety of experiences with COPD and ICS/LABA.

Physicians

There were seven physician participants in the study. This included four respirologists and three primary care physicians who generally practice full time and in urban settings. Five (71%) of these physicians described practicing in their specialty for at least 20 years and over half (n = 4, 57%) described prescribing ICS/LABA daily.

Pharmacists

There were six pharmacists interviewed for this study. Pharmacist participants were largely from community pharmacies in urban settings. Two pharmacists were located in rural settings. In all, four (66%) of the pharmacists had approximately 20 years of experience in dispensing drugs and two (34%) had over 30 years of experience. Over half of the pharmacists interviewed (n = 4, 66%) described dispensing ICS/LABA daily.

Detailed participant demographics can be found in **Appendix B**.

Key Themes Related to the Treatment of COPD with ICS/LABA

The following findings are based on the experiences and perceptions of interview participants, which have been summarized into three themes. Please note that from now on, the term "clinician" will be used to refer to both physicians and pharmacists.

The Experience of Living with COPD

- COPD Diagnosis & Risk Factors
- Disease Progression & Symptoms
- Impact on Quality of Life

The Appropriateness of COPD Treatment

- Common Treatment Escalation Strategies
- Effectiveness of ICS/LABA
- Side Effects of ICS/LABA
- Switching Between Products

Factors that Determine the Accessibility of COPD Treatment

- Improper Diagnosis
- Patient Inhaler Use
- Influences on Clinician Prescriptions
    - COPD Guidelines & Research Evidence
    - Patient Inhaler Use & the Necessity of Maintenance Medication
    - ODB Formulary & Patient Affordability
    - Drug Company Marketing
- Affordability of ICS/LABA
    - Perceived Financial Barriers
    - Limited Use Code 330

Detailed findings on each of these themes are described below.

The Experience of Living with COPD

Patient participants described their experiences of living with COPD. Specifically, participants offered insights on their COPD diagnosis and any associated risk factors, the progression of the disease, the experience of COPD symptoms, and the impact COPD has had on their quality of life (QOL).

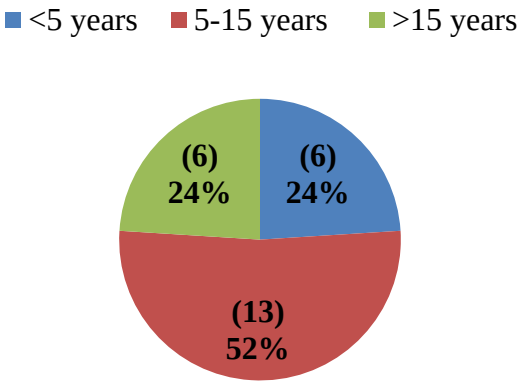
COPD Diagnosis & Risk Factors

According to participants, correctly diagnosing COPD can be challenging. About a quarter of patient participants (26%; n = 6) were diagnosed with COPD less than 5 years ago, over half (n =;52%) were diagnosed with COPD 5 to 15 years ago, and 24% (n = 6) were diagnosed over 15 years ago

(**Figure 1**). Twenty-eight percent (*n* = 7) of all participants perceived that they may have had COPD for a number of years before being diagnosed. Eight percent (*n* = 2) of participants also mentioned receiving an incorrect diagnosis of asthma a few years prior to their COPD diagnosis. Others described experiencing episodes of other respiratory conditions, such as allergies, asthma, pleurisy, mild pneumonia, and bronchitis either throughout their childhood or adult life.

Out of all patient participants, only 16% (*n* = 4) mentioned that they had never smoked and 8% (*n* = 2) mentioned that they were born with an alpha-1 antitrypsin deficiency. In addition, 12% of participants (*n* = 3) described having poor respiratory health due to workplace exposure to asbestos and mining fumes or childhood exposure to coal burning and factory fumes.

Figure 1. Number of years since COPD diagnosis



Disease Progression & Symptoms

Patient participants described the gradual decline in their ability to perform regular daily activities as a sign of COPD progression. Decreased functionality was described by a few patient participants as a result of aging with COPD. For some patient participants who were previously thought to have asthma, COPD progression enabled a correct diagnosis.

Participants considered symptom progression as another key indicator of disease progression, although some patient participants have found symptom relief in recent years by remaining active and changing their medications. The most frequently mentioned symptoms of COPD included coughing, shortness of breath, and exacerbations. Patient participants described their coughing as being extremely difficult to deal with, particularly when experiencing coughing “bouts” or “fits” or productive coughs (i.e., coughs with mucous). Environmental changes (e.g., humidity, wind, and cold) were often associated with coughing bouts. Several patient participants felt that that they were being judged by others when coughing in public.

"The coughing because it's not like when you have a cold you got a cough…The coughing could happen any time, any place. My coughing doesn't care who I am or who I'm with. At dinner time sitting with a bunch of people, if I can feel it in the back of my throat that I'm going to cough I have to excuse myself very quickly and find some quiet corner . Because the sound of a person coughing up this disgusting mess is not very attractive. And I know it's embarrassing." - Patient

Patient participants also described experiencing shortness of breath. Many patient participants elaborated on their triggers for shortness of breath, which ranged from normal daily activities (e.g., vacuuming or walking up the stairs) to more intense activities (e.g., climbing hills and other vigorous physical activities). Patient participants also described environmental triggers for shortness of breath, including paint fumes, perfume, and the weather. Several patient participants explained how shortness of breath has led them to limit or adapt their daily activities.

"My work has accommodated me that I work in an office where parking is very close now, so that's wonderful. Especially for hot days and cold windy days, so I have to consider what the weather is going to be. And when I am working, I have to think about how much I'm, how much of a load can I carry into a school, can I use a cart, is there stairs, is there meetings upstairs, you know we have one school where there's three floors and I just dread it when, oh, the meeting's on the third floor, there's no elevator, it's a really old school. So it's a constant for me, it's a, always on the back of my mind, how is this going to affect my breathing." - Patient

Exacerbations experienced by patient participants were almost always caused by infections, such as pneumonia, that produced extreme coughing and shortness of breath and required antibiotic and steroidal treatment. Most patient participants mentioned that they have had numerous emergency hospitalizations as a result of COPD exacerbations. Some patient participants described the fear associated with the experience of an exacerbation and how anxiety can worsen the symptoms associated with the exacerbation.

"When I have a flare up its something akin to trying to breathe through a straw, that's for sure. It is very difficult to deal with emotionally I find when you have a flare up, you know it makes you panic because you can't breathe. So you breathe harder and the ambulance people or the doctors are trying to get you slow your breathing down but you can't because you can't get the air in and it's almost impossible to do that. You know, to try and slow your breathing down and then you get upset and you cry, it's just creates this vicious circle, around and around and around and around. I find it horrible" - Patient

Impact on Quality of Life

Many factors related to the experience of having COPD negatively affected patients' perceived QOL. As described above, the majority of patient participants have had to adapt their lifestyles to avoid triggering COPD symptoms. Adaptations included having to adjust workload or workflow or being unable to work at all, giving up certain hobbies (e.g., painting and photography) due to the physical exertion or environmental factors (e.g., fumes or weather) involved, and having to stay indoors more often due to weather fluctuations. Many patient participants noted a significant decline over time in their ability to engage in physical activity but are attempting to remain active by making adjustments to the type and pace of activities performed so that they can relieve their COPD but also to maintain a sense of normalcy.

> *"On a sliding scale of 1-10 I feel much better than I did 2 years ago, however, not quite as good as I did about say, 6 or 9 month ago. But there is not a lot I don't do actually. I've learned to pace myself. Like stairs still, when I come up stairs I'm a little I'm not totally out of breath and for long bouts of walking I have to stop sometimes and take a puffer. Hills, I pretty much try to avoid if I can."*
>
> *- Patient*

As mentioned above, patient participants described experiencing stress, anxiety, and fear related to exacerbations of COPD symptoms. They also described ways in which their COPD experience has affected their perceived QOL by affecting their mental health. The issues discussed by patient participants ranged from having anxiety related to certain events (e.g., not having appropriate medication available when needed) to having major depressive episodes. One participant elaborated on how the experience of having COPD has changed her perspective on life.

> *"Well I could think of a lot pleasanter things to do then to live with this disease. It's taught me so much… it teaches you all about anger. It teaches you about depression. It makes you feel useless. It brings anxiety into your life. You no longer have real independence, it makes you less than you can be but… I am very thankful that there are medications that make it a little better because I am just… its… it teaches you the value of every day. Teaches you about self-pity, because every time something happens you have to go through that but you have to get a hold of it. It teaches you about lonely… teaches you about picking yourself up and carrying on because you get lots of practice doing that. One of the things that I'm learning now is learning to ask for help, which is probably one for the hardest things …" - Patient*

Patient participants also discussed how the impact of COPD on social networks and support has affected their perceived QOL. For example, some patients discussed the difficulty of keeping up with friends as their COPD progresses. Despite their disease severity, however, many of these patient participants stay connected to friends and attempt to participate in both small (e.g., dinner parties) and large (e.g., travelling tours) gatherings to maintain a sense of normalcy. One patient participant mentioned that having COPD has provided opportunities to connect with people in different ways.

"I still have pretty good quality of life considering, you know. And that allows me to, in turn. I am not able to work anymore but I can do… put in a little bit of volunteer work by internet, for example. Which has a volume, you know. I am working with doing some volunteer, mostly I write. I do some policy work and work with people primarily in developing countries and with international organizations."- Patient

Many patient participants also discussed the impact of COPD on family members and caregivers. In some cases, patient participants perceived that their family members experience stress and anxiety as a result of the patient's COPD and often internalize the experience more negatively (i.e., "take it harder") than the patient does. For some patient participants, their family and friends act as caregivers by either supporting the patient in their spare time or by paying for home care services or residence in retirement homes. Spouses of patient participants often provide daily support to ensure that patients take their medications and can perform activities of daily living. Participants noted that caregivers of patients with severe COPD may experience drastic life changes as a result of the patient's disease progression.

"Oh, It's huge it has changed our life completely. When he was first was diagnosed I was still working, you know, it was fine, he was doing everything… he did all the washing, all the laundry and the cooking… not the cleaning, he found it difficult to push a vacuum and stuff but he doing everything. Once he went on oxygen that did continue up until 2008. He still did a lot, again, it took him longer but he wanted to do it. In 2008 I left my job because we had an incident where we were away on vacation and he almost died from CO2 retention. So he was in Albany, New York for a week in intensive care and we decided at that point that I… we should re think this working until I get my pension. So I left work early so that I could enjoy the time with him. So that changed, once I quit working, then I did everything and certainly the last 2 years I've done a lot more… like he used to… we have the oxygen delivered to the garage, he used to go out and bring in his tanks, now I do that. I don't like him to waste the bit of energy that he has stuff that I can do for him. So its change our lives quite a bit. We used to go out quite a bit, we don't now because it just more difficult, so it's easier to have people here than to drag him out somewhere. So we just modified things but you do what you have to do."- Caregiver

Still, for many patient participants, the effect of COPD on social networks and support was perceived to be minimal as many patients attempt to normalize the disease by making small adaptations to their lifestyles and being open and honest with their loved ones about their health status. Some patient participants discussed the support they receive from health care providers and patient education services to help them cope with their disease as a resource that has improved their perceived QOL.

The Appropriateness of COPD Treatment

This theme describes perceptions of patient, physician, and pharmacist participants on appropriate treatment strategies for alleviating the symptoms and progression of COPD. The appropriateness of COPD treatment is described in terms of common treatment escalation strategies and the particular role of ICS/LABA.

Common Treatment Escalation Strategies

Physician participants elaborated on approaches to prescribing medication to COPD patients with mild, moderate, and severe disease. Most physician participants described starting patients with mild disease on short-acting beta agonist (SABA) products, although they mentioned that most of their COPD patients require an adjunct medication rather than SABA alone. The second line of drugs that physician participants most often prescribe to COPD patients are long-acting muscarinic agents (LAMAs), such as Spiriva® and Seebri®. With more progressive disease, some physician participants prescribe long-acting beta agonists (LABAs) in conjunction with LAMAs and use SABAs as rescue medications. ICS/LABA combinations are reserved for patients with more severe disease and are usually prescribed as part of triple therapy (i.e., ICS, LABA, LAMA) with SABA prescribed as a rescue medication.

Although it appears that there is a standard method of escalating COPD treatment, physician participants highlighted several factors that affect the selection of appropriate treatments for specific COPD patients. First, some physicians described the different COPD phenotypes and how this may determine the appropriateness of certain medications. Asthma phenotypes were described as being more responsive to oral and inhaled steroidal therapy whereas bronchitis phenotypes were described as being less responsive to these steroids when used alone or in combination with LABAs. (We note that the use of inhaled steroids alone is not indicated for COPD patients.) Second, physician participants discussed an existing "steroid philosophy," where differences in opinions between physicians on steroids can affect when steroid therapy is introduced to patient treatment regimens. Physician participants perceived that there are physicians who buy in to the long-term use of inhaled steroids when they witness the effects of steroid therapy on acute exacerbations, which leads them to prescribe ICS/LABA combination products far earlier or for longer than needed.

"Well, I think I'd like to know they have a chronic steroid responsive component. I think a lot of these patients get on it when they have an acute steroid responsive component. They have an infection, they go on steroids, they feel better, they say, "Aha! Steroids help the patient." Yeah, it helped the patient short term, but does it help them in the long term? And I do a lot of reverse steroid trials, where somebody comes into me, in my clinic or my office and they're Advair® or they're on Flovent® or they're on Pulmicort® or Symbicort® and they stop it for a few weeks and repeat their spirometry and see if there's any difference, and often times, there isn't, which tells me, you don't need this regularly, but yes, when you get a head cold and it goes into your chest, by all means go back on it, but that you don't need to take it everyday for the rest of your life. But much, I think, a lot of the problem I think is people get on it and every often, nobody thinks of stopping it, despite the enormous cost of these medications. "- Physician

Most physician participants were wary of the effects of steroids and therefore prescribed ICS/LABA only when LABA/LAMA treatment with SABA used as rescue was no longer effective in reducing exacerbation of symptoms. Finally, method of medication delivery may influence the types of medications prescribed. For example, one physician participant described LAMA products as easier for patients to use than the ICS/LABA products because patients need to use LAMA products only once each day.

Pharmacist participants found it difficult to identify which patients who pick up medications for ICS/LABA have COPD. Most of them were able to confirm, however, that among those patients who are known to have COPD, the following treatment regimens are commonly seen in their pharmacy settings: 1) LAMA with SABA as rescue, 2) ICS/LABA prescribed with LAMAs and SABA as rescue, and 3) ICS/LABA with SABA as rescue. Many pharmacist participants described LAMAs with SABA as rescue as the most frequently observed treatment regimen in recent years. One pharmacist participant expressed concern when ICS/LABA was prescribed without a patient having received a prescription for LAMAs first.

"What worries me is when I see someone an Advair® or Symbicort® and then a, you know, a short-acting Ventolin® along with it, and I suspect they might have COPD but I don't know and I feel like, "Jeez, have you tried the anti-cholinergic? Why don't we have an anti-cholinergic on board?" That's the one that leaves me... if they're on the tiotropium and we're now adding an ICS/LABA combination I feel better, but if I suspect, "Jeez, I wonder if this guy has COPD?" or a lady has COPD, then I worry if I don't see the anti-cholinergic."- Pharmacist

Of the patient participants included in our sample, 80% (*n* = 20) were on "triple therapy" consisting of a ICS/LABA combination product in

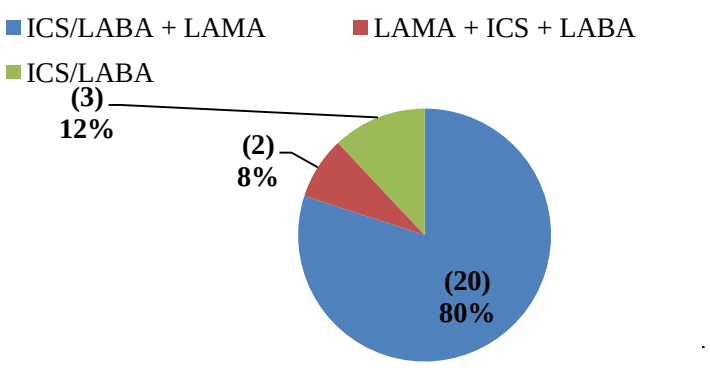


Figure 2. Types of medications used by patient participants

addition to a LAMA (Figure 2). Twelve percent (*n* = 3) were on an ICS/LABA combination product only, and 8% (*n* = 2) were on ICS, LABA, and LAMA (no combination products). Twelve percent (*n* = 3) of patient participants indicated that they had previous experience using ICS alone (i.e., not as part of a combination product); this may have been related to the fact that a few patient participants were diagnosed with asthma before their COPD diagnosis. Thirty-two percent (*n* = 8) of participants described that they are currently using supplemental oxygen. When asked about the order in which medications were initiated as part of their treatment, there was much variability in how patients had arrived at their current treatment regimens. Most patient participants were started on SABA products but may have also used ICS products, such as Pulmicort, which were often switched to an ICS/LABA combination product. Patient participants who were on LAMA products initiated LAMAs either before, after, or at the same time as initiating their ICS/LABA combination products. Some patient participants were put on an ICS/LABA product right away and had never used any other product other than SABA for rescue.

> *"Actually my GP first prescribed inhalers. Notably, I started with Ventolin® for emergencies and then Symbicort® on a regular basis. I guess Symbicort®, the dosage at the time was 100-2, 2 puffs twice a day, that's what I started with. I have been using that, I have been using Symbicort® for at least 10 years let's say, at least 10 years of a low dose."* Patient

Effectiveness of ICS/LABA

Participants were asked to assess the effectiveness of ICS/LABA based on their perceptions of functionality, effects on quality of life, and improvement in lung function. Participants differed in their perceptions of the effectiveness of ICS/LABA products in comparison to that of other COPD drugs and to no treatment. Participants generally viewed COPD therapies, such as ICS/LABA, to be useful for preventing exacerbations but had mixed views on the effect of ICS/LABA on quality of life.

Patient participants generally had difficulty describing the effectiveness of ICS/LABA products primarily because it was difficult to isolate the effects of ICS/LABA from those of other drugs. Since most patient participants were taking multiple drugs at the same time or taking additional actions to control their COPD symptoms (e.g., attending pulmonary rehabilitation, removing environmental triggers, or adjusting lifestyle), improvements in overall health could not be attributed solely to ICS/LABA use. Moreover, some patients had been using ICS/LABA products for so long that they were no longer able to compare their current health to their health before they began using ICS/LABA products.

> *"Well, I don't know how to answer that because I've always been taking it ever since I had the operation, so I don't know what it would be like without it."* - Patient

This finding was echoed by many physician participants, who were unsure about whether there are any benefits to adding the ICS/LABA combination product to a treatment regimen. For most physician participants, ICS/LABA is prescribed to patients when their COPD has advanced to a point where any benefits of therapy become "marginal" benefits. Similar to patients, some physician participants were also unable to differentiate between the effectiveness of ICS/LABA products versus other medications and lifestyle changes or activities.

> *"It's pretty hard to separate that out from the effectiveness of Spiriva® in doing the same because I use them both. I, again, don't have enough patients to be able to tell you, like, "This population has just been on Spiriva® and this has been on both," and compare their rates of exacerbation, because it's usually confounded by other things like their lifestyle and, you know, just their health access or health-seeking behaviour in general." - Physician*

One physician recognized the benefit of the long-acting component of the ICS/LABA product but questioned the added benefit of the ICS component and whether this was needed. Another physician noted that for steroid-responsive patients, the ICS/LABA combination is efficacious as most of these patients would benefit from the long-acting beta agonist component. Some physicians do see that patients can be responsive to ICS/LABA products and experience improvement in their QOL, which is why they continue to prescribe these drugs.

> *"…we do believe that these medications do reduce exacerbations and do have some effect on mortality, but it's not sort of ingrained in stone, and it depends on each individual patient. So my personal practice kind of supports that conclusion, there are some people who respond to the medication quite nicely, combination of ICS/LABA…About 20% – that's a minimum 20% – of patients with COPD, if not more, actually have a combination of COPD and asthma so these people are more apt to respond to any kind of a medication containing a steroid, so that's why I cannot just disregard the medication completely, and I do have to say that it is effective, moderately effective, can be very effective in some patients depending on the phenotype."- Physician*

> *"You know, I think it's the LABA component of these drugs that would improve quality of life. I think the inhaled steroids really is more to reducing exacerbations which may, by default, do that. But that data is not as strong as people consider it to be, so in general, as I say, I think we use them out of frustration that we don't have anything else that's really effective, and a lot of patients are on what we call triple therapy, which would be Spiriva® plus an ICS/LABA combination therapy." Physician*

Patients who were able to speak to the effectiveness of ICS/LABA combination products often compared their current health to their health prior to using ICS/LABA products and defined the effectiveness of the drugs in multiple ways. For example, patient participants described experiencing fewer exacerbations and episodes of shortness of breath. In addition, some patients noted that they have had fewer emergency hospitalizations since they began their ICS/LABA

treatment. One patient participant noted that his lung function tests improved after using Symbicort®, degraded when he stopped using the product, and returned to an improved state after initiating use again. Most notably, the use of medication has helped improve overall QOL for most patient participants in the sense that they are able to perform their activities of daily living.

> *"I can tell you, in all the areas, ability to breathe, my ability to… I exercise, my ability to walk quickly, run upstairs, all these things and overall sense of energy and wellbeing. Huge, huge difference, sorry I cannot quantify it, but just to say it affected all of those areas."" - Patient*

Side effects of ICS/LABA

Patient participants described many side effects of their COPD treatment regimen, but similar to their perceptions of ICS/LABA effectiveness, they were generally unable to specify which of these side effects stemmed from ICS/LABA use. The most common side effects reported included hoarseness, thrush, and dry mouth. Some patient participants also discussed experiencing anemia, osteopenia, cataracts, and insomnia that were attributed to ICS/LABA use. Physician and pharmacist participants described having observed these side effects in patients, which occur as a result of long-term steroid use (both inhaled and oral steroids). Most patient participants did not consider their side effects severe and were willing to experience them to gain the benefits of the drugs they were taking for their COPD treatment.

> *"He bruises very easy, other than those kinds of things like he feels ok taking them. You have to remember, that's very difficult… he's been trying to come up with a way you could put a counter or something on the… you know, if you can reset it to the number of puffs every day you could keep track a bit easier . But I don't think that has affected him much as the COPD itself. Taking the medication, you can deal with that, it's the actual disease that has made the difference." - Caregiver*

Some patient participants did not report experiencing any side effects at all. A few physicians described skin bruising as a rare side effect whereas others described it as a common side effect among their patients. A few physician participants were also concerned about the link between ICS/LABA use and an increase in the risk of pneumonia.

> *"Well the steroids, maybe the hoarseness and the thrush, the only things that I really worry about, I mean there's some evidence that high-dose inhaled steroids can cause things like osteoporosis and premature cataracts and bruising of the skin. I'm sure it happens, but I don't believe that, it's not as big a deal to me in most patients." - Physician*

> *"I think again to say that the major thing I'd be worried about is the people that have a history or have an episode of pneumonia when they're on these medications, and I think that's something that we'll be concerned about. And again the skin bruising is something that I can visually see on my own patients." - Physician*

Switching between products

Switching between ICS/LABA products was discussed briefly across all participant groups. Overall, patients, physicians, and pharmacists all noted that product switching (e.g., switching from Advair® to Symbicort® and vice versa) was rare, but when this did happen, it was almost always due to side effects or dose delivery considerations rather than to product efficacy.

Factors that Determine the Accessibility of COPD Treatment

Improper Diagnosis

Participants from both patient and clinician groups described the diagnostic challenges of COPD. Some physician participants admitted having difficulty with both remembering the correct diagnostic criteria for patients who present with respiratory symptoms and interpreting spirometry results. In some cases, primary care physicians described experiences of incorrectly diagnosing patients with COPD and prescribing them combination drugs, such as Advair® and Symbicort®, which were not necessary for their condition.

> *"I think the spirometry results come out of a computer. The computers need to be changed so that the one element that's important, when FEV1 to FEC post-bronchodilator is highlighted, and those that are less than 70 are in red, and if they're not red they don't have COPD. That's it. It's too complicated. The printout's too complicated. The printout is too complicated to interpret" –Primary Care Physician*

> *"So I think there's probably a problem in terms of accurate identification. I know what the criteria are, and for some reason I just… you know, the spirometry tests come back and they don't… they say, "Oh, probably has COPD," but when you look at the criteria they don't meet the criteria, or I didn't look at the criteria, or forgot what the criteria were and mislabelling half." –Primary Care Physician*

Some repirologists also remarked that a large number of the patients who are referred to them with a COPD diganosis have never been given a spirometry test to confirm the diagnosis. In addition to the overdiagnosis of COPD, participants reported concerns about underdiagnosis or late diagnosis (described previously). Respirologist participants expressed a concern that late diagnosis has a direct impact on access to treatment because COPD patients who are treated early have a greater chance of receiving appropriate and necessary medication. Since COPD is a progressive disease, those who receive a late diagnosis may see a more rapid decline in lung function.

"Bronchodilators certainly don't decrease the loss of lung function unless we get patients early enough and then the UPLIFT/GOLD 2 stage trials there was a slight slowing lung in loss of lung function, and that may well happen if we catch COPD patients early enough. So my plea is that we should be diagnosing COPD earlier, which means patients should be getting spirometry" – Respirologist

Patient Comfort Level with Diskus and Metered Dose Inhaler Use

Patients who are comfortable with administering their COPD medication are more likely to take the appropriate medication dosage. This finding was consistent across all participant groups. Pharmacists in small pharmacies described having the time to sit down with patients to teach them how to operate the metered dose or diskus inhaler. In general, participants from both clinician and patient groups agreed that the diskus products are easier to use than the metered dose inhalers. Pharmacist participants in busier pharmacies described that they do not always have the time to teach first-time patients how to use these medications and that they have concerns that some elderly patients may not be appropriately accessing the medication they need.

"You do hear back from the patient that they're not feeling any better having used the device, and then we need to ask them to come back to the pharmacy so that we see exactly how they're using it and what would be the reason why they're not getting the maximum out of the device that they should be getting. So they do need to come back…and sometimes some come back, sometimes some don't, so that's the challenge that we have" –Pharmacist

Most clinicians recounted that they do not take the time to sit down with their patient and explain how to use COPD medications; however, a few respirologist participants have instituted a brief education program as part of standard care for any new referrals. Overall, most participants (including patients) noted that the products are relatively easy to use when patients receive proper instructions. The Advair Diskus® inhaler was identified as a very commonly prescribed drug because it is easier to use than Symbicort® and there is less concern that the patient may not be administering the medication correctly.

Influences on Physician Prescriptions

Physician participants were asked to describe the factors that influence their prescription choices for their COPD patients. There were a number of issues identified by both respirologists and primary care physicians that have an impact on a patient's access to COPD medications, such as ICS/LABA products.

Nearly all respirologists and primary care physcians described that they refer to either the GOLD or Canadian Thoracic Society guidelines for COPD treatment. Some primary care physician participants have an application in their electronic medical record (EMR) that is based on the GOLD guidelines but operates under the assumption that the patient has already been correctly diagnosed with COPD. In addition, respirologist participants said that they incorporate evidence from specific research studies to influence their decisions on COPD prescribing. For example, they mentioned the

TORCH trial, which has influenced Advair® precription; the PATHOS trial, which has influenced Symbicort® prescription; and the OPTIMAL study, which has influenced the prescription of inhaled steroid products in patients who are frequent exacerbaters. Respirologist participants did mention, however, that the way in which clinicians interpret data from research studies may differ and have varied impacts on prescription.

> *"I think that after TORCH, people's behaviour changed because depending on how you interpret the results of TORCH, some people felt that a p-value of 0.052 was close enough to a mortality advantage that there's a mortality advantage with the combined ICS/LABA product, which outweighs any potential increased risk of pneumonia, which is another data set that's been out there that's shown in several retrospective studies. So I think partly it's the marketing and partly it's how one interprets the results of TORCH." –Respirologist*

Clinician participants also indicated that they take certain patient factors into account when prescribing treatment. For example, if a patient is using a SABA inhaler (e.g., salbutamol [Ventolin ®]) more than three times a week, some participants would consider adding a long-acting maintenance puffer to their regimen. If a patient is more comfortable with a diskus product than a metered dose inhaler, then the clinican may prefer to prescribe an Advair® or Ventolin Diskus®. In addition, some clinician participants described using a strategy called "reverse trials" on stable patients who have been on the same treatment for several years. This strategy involves ceasing maintenance medications for a short period of time and then conducting a spirometry test to determine whether there is still need for certain medications, particularly those that could have long-term side effects (e.g., ICS/LABA). These participants also explained, however, that the reverse trial strategy is controversial and not used by the majority of physicians.

> *"I think, a lot of the problem I think is people get on it and every often, nobody thinks of stopping it, despite the enormous cost of these medications." –Respirologist*

> *"a lot of the patients you're dealing with are elderly, with mild dementia, who don't speak English, and it's very important to get them on the absolutely easiest device to use. And a diskus is the easiest device to use." –Respirologist*

Most physician participants described that the ODB formulary does not have a strong influence on their COPD prescription habits because the majority of their patients are over the age of 65 years and are eligible for coverage through ODB. In addition, physician participants reported that many of their patients have an asthma component to their COPD and therefore would be eligible for the Limited Use code for asthma. For the small group of patients who are under the age of 65 years, most pay with private insurance and those who do not have private insurance are given samples when available.

"I think all of us write code 330 interchangeably in asthma and COPD patients. We all know that it's for asthma patients, but we also know that there's a wealth of data that supports this in COPD, and to my mind, it would be, there would be no argument that could win, that could say that you should not have, so you got to practice according to best practice." –Respirologist

One physician participant described that the combination of certain patient factors and the list of drugs on the formulary can have an impact on the prescription of ICS/LABA products. For example, this participant noted that the Ventolin Diskus® is not on the formulary but is easy for patients to use. Salbutamol and terbutaline (Bricanyl®) are not available in diskus form but Bricanyl® is available as a Turbuhaler®. Thus, to ensure that an ODB-funded patient is properly administering a beta-agonist component regularly, a physician may prescribe an Advair Diskus® instead of a Flovent® with PRN salbutamol regardless of whether the patient experiences frequent exacerbations and is in actual need of regular combination ICS/LABA treatment. The large number of COPD patients on an Advair Diskus® was a concern mentioned by respirologists, pharmacists, and primary care physicians.

A few clinicians perceived that drug company marketing strategies have greatly increased the prescription of ICS/LABA and other COPD treatment products in Ontario. One physician described, for example, that drug company representatives have offered training and resoures for family health teams to implement respiratory education and COPD screening programs. These include screening questionnaires, pamphlets for patients, and spirometry machines. There was concern among clinician participants about the overprescription of ICS/LABA products for patients who do not need them because of the financial cost to the system and the side effects of long-term steroid use.

"the drug reps have been in several times recently trying to really push their puffers, and they're also trying to really push respiratory programs, and our family health teams are implementing respiratory programs – like a lot of FHTs in Ontario – and we're starting to do more spirometry, and I think that's a bit of a concern because the other thing that's been pushed is screening, so there's a questionnaire for screening, you know, do they smoke, are they over 40, and do they cough, etc., so that's going to lead to a very large amount of over-diagnosis and use of drugs." –Primary Care Physician

"I don't think any of us feel any insecurity about the, you know, the strength of the evidence supporting that approach and the guidelines would support that as well, in the right population: patients who are frequent exacerbators who are severe. And I will say that the combination product because of the marketing campaign by the companies that produce the two products are used often first-line, particularly in primary care and also in many of my colleagues; many of my colleagues do not prescribe long-acting beta agonists in isolation. They never do. If they go there, they go to the combo right away." –Respirologist

Affordability of ICS/LABA Products

When participants were asked to describe affordability challenges for COPD patients, most participants from all three groups reported that there were no significant barriers. This is because the majority of patient participants in this study and those in the practice populations of our clinician participants are over the age of 65 years and receive coverage for medication through Ontario Drug Benefit. However, a few clinician participants reported that there is a small proportion of COPD patients under 65 years of age who do not have private coverage and experience substantial obstacles in accessing appropriate treatment. These patients are more likely to have exacerbations and frequent hospital visits because they cannot afford to take maintenance medications, such as ICS/LABA products.

> *"I'm so afraid that one of these times that I can't afford the drug that I'm going to die because I can't afford to buy it. I don't want to die because I'm only 55. You know the drugs is just expensive, I just can't afford it. I just don't know what the drug companies think, that all people are rich or that all people have drug coverage or what but I'm just…. being on worker comp they don't pay you very much money to begin with. So I just don't have all the money to buy all of these drugs for my breathing." –Patient*

All clinician participants (i.e., respirologists, primary care physicians, and pharmacists) noted that physicians use the LU code 330 to obtain publically-funded ICS/LABA products for their patients. Some mentioned that the LU code is automatically printed off through their EMR system for any ICS/LABA prescription for patients over 65 years of age regardless of whether the patient has COPD or asthma.

> *"when the medication is issued the LU code is issued together with it – I don't even know it, it is issued – so all the pharmacist needs is that number, which is part of the prescription, so there's no human thought that goes beyond it. The LU system does not work." –Physician*

Some clinician participants were concerned that the LU code is not being used for its intended purpose. They explained that they believe the purpose of the code is to limit the overprescription of ICS/LABA drugs, which are indicated for only a subset of severe COPD patients. However, in practice, there is no true monitoring system to check whether patients who do not need this drug are receiving coverage for it. These same participants were also honest about the fact that they use the LU code themselves because they are left with no alternative options for patients over 65 years of age who require treatment and do not have coverage for necessary medication. Physician participants perceived that there would be great access issues for many of their patients if they were not willing to attribute the incorrect LU code to ICS/LABA prescriptions.

> *"I have to make sure that my patient gets the right medication for their problem, and if I think they need ICS/LABA then that little white lie – again I hope this doesn't come back to bite me if this really must be anonymous – but that little white lie is going to help my patients then I'm willing to do so" – Physician*

> *"at least it should be known that there's a spot check mechanism so it doesn't get abused. I would favor spot check and maybe you're liberalizing the indication, so it's easier for people to get on it and need it, but on the other hand, you're making sure that only those people are on it and that… because I think that if you, I think the current definition is a bit restrictive at times, but I think if you should spot check, and it's the same with all the medications of limited use. There's no mechanism, they just come up with these rules, and so after a while, it becomes sort of part of the culture, everybody's abusing it." –Physician*

Some pharmacist participants described that they are occaisonally put in an awkward position when a patient submits a prescription with the LU code and they have reason to believe that the patient has a COPD diagnosis with no asthma components.

Discussion

Key Findings

Our study highlights many key experiences and perceptions related to ICS/LABA prescription and use; we found several factors that may be affecting appropriate use and access. One key finding was that ICS/LABA is frequently prescribed to patients with COPD who are ODB eligible even though there is no listing for ICS/LABA on the formulary for COPD indications. Physicians may resort to using the LU code 330 for asthma to access these drugs for their COPD patients. Another important finding was that the challenge of diagnosing COPD can affect both the appropriateness of treatment and access to appropriate medications. Furthermore, we found that patients often receive ICS/LABA medications early in their COPD diagnosis even though both physicians and pharmacists have reservations about the appropriateness of these prescriptions and the benefits of the drug class.

Health Equity Considerations

The findings from this study highlight that access to ICS/LABA is not an issue for ODB-eligible patients only because physicians are circumventing the absence of a COPD listing for ICS/LABA by using an asthma LU code. While this facilitates access to these drugs for the majority of COPD patients, this may not be the most appropriate method of accessing ICS/LABA. In addition, patients under the age of 65 years who do not have access to third-party coverage (and are not ODB eligible), face significant financial barriers to accessing ICS/LABA products because of their cost. ICS/LABA samples may be given to these patients by their physicians to help facilitate access, but this method of dispensing drugs is not a sustainable solution for patients in need.

Limitations

It should be noted that qualitative findings are not representative of the general population of individuals from which our study sample was drawn. For example, participants who responded to our interview requests may have been more likely than non-responders to be vocal about discussing issues related to the treatment of COPD. (e.g., participants could have been involved in COPD advocacy initiatives). In addition, many of our physician participants were COPD experts or had a particular interest in COPD. To limit bias in our samples, we used negative case sampling, which involves introducing different viewpoints by selecting interview participants who differ from the response trend observed in the recruited sample to date.

Conclusions

The findings from the qualitative study of the ICS/LABA drug class review informed the methods of other ODPRN research units that are conducting studies as part of the review. Moreover, our qualitative study helped to contextualize the results of the systematic review, pharmacoepidemiological analysis, and environmental scan performed within the separate research units of the ICS/LABA for COPD drug class review. On a broader scale, our study findings fill a gap in knowledge on access to ICS/LABA combination products and how this may be affected by physician and patient perceptions of these drugs and diagnostic challenges. Overall, our findings shed light on the experiences of prescribing, dispensing, and using ICS/LABA for COPD treatment. They also unveil important information that can affect how patients in need can access these drugs across Ontario.

References

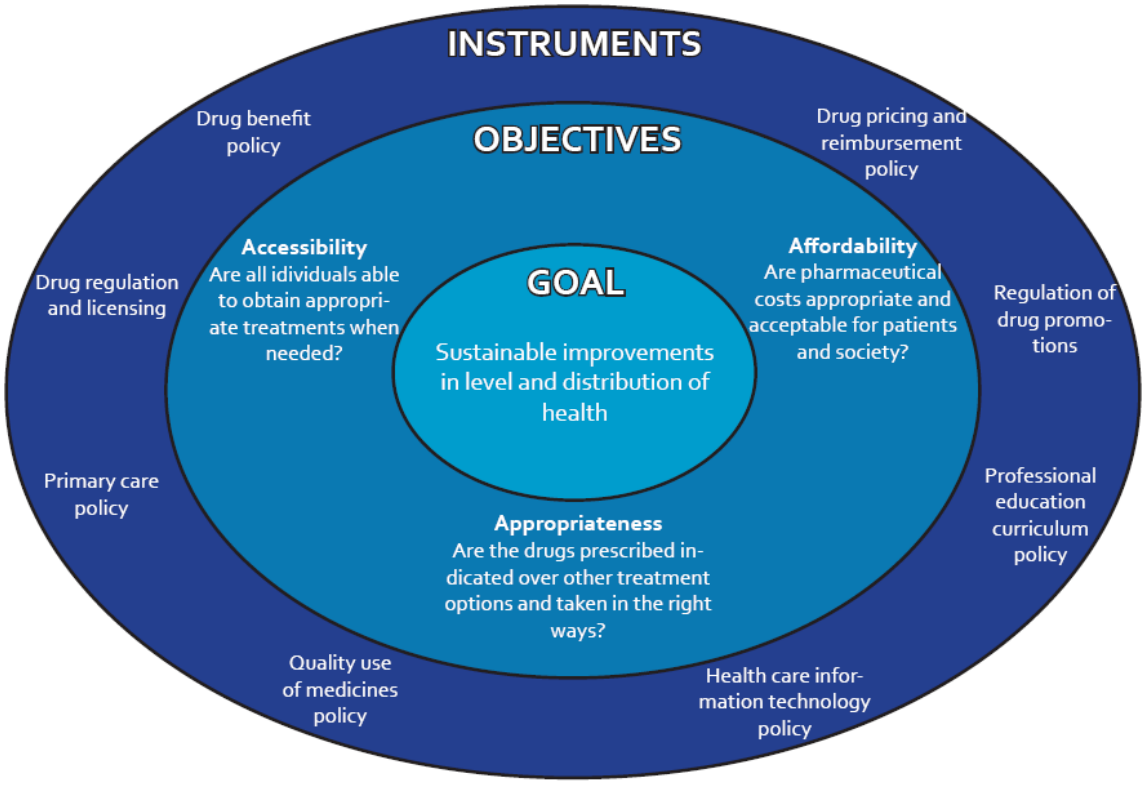
Kuzel, A. J. (1999). Sampling in qualitative inquiry. In B.F. Crabtree (2nd ed.), *Doing qualitative research* (pp. 33-45). Thousand Oaks, CA: Sage Publications.

Morgan, S., Kennedy, J., Boothe, K., Mcmahon, M., Watson, D., & Roughead, E. (2009). Toward an Understanding of High Performance Pharmaceutical Policy Systems: A "Triple-A" Framework and Example Analysis. *The Open Health Services and Policy Journal TOHSPJ*, 2(1), 1-9. doi:10.2174/1874924000902010001

O'Donnell, D. E., Aaron, S., Bourbeau, J., Hernandez, P., Marciniuk, D. D., Balter, M., . . . Voduc, N. (2007). Canadian Thoracic Society Recommendations for Management of Chronic Obstructive Pulmonary Disease – 2007 Update. *Canadian Respiratory Journal*, 14(Suppl b). doi:10.1155/2007/830570

Ritchie, J., & Spencer, L. (n.d.). Qualitative data analysis for applied policy research. *Analyzing Qualitative Data*, 173-194. doi:10.4324/9780203413081_chapter_9

Appendix A: "Triple-A" Framework for Pharmaceutical Policy Analysis



Adapted from: Morgan S, Kennedy J, Boothe K, McMahon M, Watson D and Roughead E. (2009) Toward an Understanding of High Performance Pharmaceutical Policy Systems: A "Triple-A" Framework and Example Analysis. *Open Health Services and Policy Journal:2;* 1-9

Appendix B: Participant Characteristics and Demographics

Patients

Demographic Characteristic (n=25)	n	%
Gender		
Female	12	48%
Male	13	52%
Age		
25 -34	0	0%
35-44	0	0%
45-54	1	4%
55-64	6	24%
65+	18	72%
Employment Status		
Full-time	1	4%
Part-time	3	12%
Unemployed (retired, disability)	21	84%
Years Since COPD Diagnosis		
<5	6	24%
5-15	13	52%
>15	6	24%
Past Smoker?		
Yes	21	84%
No	4	16%

Physicians (Respirologists and Primary Care)

Demographic Characteristic (n=7)	n	%
Years of practice		
<5	1	14%
5-15	0	0%
>15	6	86%
Type of Practice		
Full-time	5	71%
Part-time	2	29%
Geographic Location		
Urban	6	86%
Suburban	1	14%
Frequency of Prescribing ICS/LABA		
Daily	4	57%
Weekly	1	14%
Monthly	1	14%
Annually	1	14%

Pharmacists

Demographic Characteristic (n=6)	n	%
Years of practice		
5-15	0	0%
>15	6	100%
Type of Practice		
Full-time	6	100%
Geographic Location		
Urban	2	33%
Suburban	2	33%
Rural	2	33%
Frequency of Prescribing ICS/LABA		

Daily	5	83%
Weekly	1	17%