Buccal Hydromorphone Syrup for Managing Dyspnea in Idiopathic Pulmonary Fibrosis

Shannon Fong, MD1, Janice Richman-Eisenstat, MD2, and Meena Kalluri, MD2

Abstract
Context: Dyspnea is a highly distressing symptom that characterizes idiopathic pulmonary fibrosis (IPF), a common idiopathic interstitial lung disease (ILD) with a high symptom burden, poor quality of life, and early mortality. Though opioids are mentioned in guidelines for dyspnea management, guidance on how and when to initiate opioids is lacking. Different pharmacologic strategies are needed to address different types of dyspnea (baseline, incident, and crisis). Due to a longer onset of action, the oral route (swallowed) may be less effective for prevention of incident dyspnea or for rapid relief of crisis dyspnea, prompting the use of alternative drug delivery strategies for self-management. We inadvertently discovered the efficacy of buccal administration of low dose, low volume hydromorphone oral syrup for dyspnea management in ILD, which has not been previously reported in the literature. Case Series: We describe our approach to dyspnea assessment and management in IPF, including use of the Multidimensional Dyspnea Scale (MDDS), a novel instrument yet to be validated that we developed to better identify and categorize dyspnea into the types experienced by a patient with IPF over the course of a day. We then describe how buccal hydromorphone oral syrup is initiated and titrated for dyspnea management in 3 patients at different points in their disease trajectory. Conclusion: Buccal hydromorphone oral syrup is effective for dyspnea management across the spectrum of IPF. When integrated into a patient-centered algorithm for symptom assessment and management, it allows for rapid and easy self-management of dyspnea by patients and their caregivers.

Keywords
dyspnea, idiopathic pulmonary fibrosis, buccal hydromorphone

Introduction
Pervasive dyspnea characterizes idiopathic pulmonary fibrosis (IPF), a common idiopathic progressive fibrosing interstitial lung disease (ILD) with a high symptom burden, poor health related quality of life (HrQoL), and early mortality. With disease progression, dyspnea intensifies and worsens functional activity.1 Early recognition and management of dyspnea is needed to preserve function and maximize HrQoL earlier in the disease trajectory as well as at the end of life to improve quality of death and dying in IPF. While the urgent need for dyspnea management across the IPF spectrum is recognized, practical guidance specifically about when and how to initiate opioids is lacking.2,3 In this case series we describe our approach to using buccal opioids guided by a novel clinical instrument yet to be validated, the Multidimensional Dyspnea Scale [MDDS; contact author (MK) for access]. The use of this approach within our Multidisciplinary Collaborative Care (MDC) clinic model has led to early detection and treatment of dyspnea, improved end of life care and reduced hospitalizations and costs.4-6,7

The MDDS was developed as a clinical tool to facilitate identification and categorization of dyspnea into 3 types experienced by a patient over the course of a regular day. These categories include: baseline dyspnea which occurs when resting, talking or eating; incident or episodic dyspnea, which is anticipated with a particular activity; and crisis dyspnea, which is unanticipated.9 Patients rate the intensity of dyspnea related to different activities during their day, assigning a value from 0 to 10 to each item on a linear scale, where 0 means no breathlessness and 10 is the most intense. The MDDS scores

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guide development of a patient-centered algorithm for symptom management based on the activity, timing and circumstance when dyspnea occurs. Non-pharmacologic and pharmacologic strategies are added iteratively and adjusted to reduce MDDS scores (Table 1). Opioid initiation starts with low dose hydromorphone oral syrup (1 mg/ml) delivered via the oral route (swallowed) to control baseline dyspnea (target MDDS <2-3/10), and via the buccal route for reduction of incident dyspnea (target MDDS <4-5/10) and for rapid relief of crisis dyspnea (MDDS ≥ 8). To our knowledge, the use of hydromorphone oral syrup via the buccal route for dyspnea management in ILD has not been previously reported in the literature. Although there is limited data regarding buccal hydromorphone, the existing literature suggests that sublingual absorption of hydromorphone is less than that of more lipophilic opioids such as fentanyl. However, our clinical experience suggests that it is indeed effective and absorbed. Here, we describe a case series of 3 patients at different stages of IPF where the MDDS guided the use of buccal hydromorphone oral syrup for dyspnea self-management, initiated at time points ranging 6 months to 5 years prior to death.

### Table 1. Patient-Centered Algorithm for Dyspnea Management.

<table>
<thead>
<tr>
<th>Steps</th>
<th>Selected examples</th>
</tr>
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<tbody>
<tr>
<td>1. Confirm primary diagnosis</td>
<td>CHF, arrhythmia, ischemic heart disease</td>
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<tr>
<td>2. Assessment and optimization of comorbidities</td>
<td>Obstructive sleep apnea</td>
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<td></td>
<td>Mood, anxiety, depression</td>
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<td></td>
<td>Gastrointestinal symptoms (GERD, constipation)</td>
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<td></td>
<td>Postnasal drip, sinus congestion</td>
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<td></td>
<td>Infection mitigation (eg, vaccinations)</td>
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<tr>
<td>3. Use of comprehensive dyspnea instrument [Multidimensional Dyspnea Scale; contact author (MK) for access]</td>
<td>Categorize and rate types of dyspnea: baseline, incident (episodic) and crisis</td>
</tr>
<tr>
<td></td>
<td>Intensity: mild (2-3/10), moderate (4-5/10) or severe (6-7). Crisis: 8-10/10.</td>
</tr>
<tr>
<td>4. Initiate non-pharmacologic measures</td>
<td>Fan, air circulation</td>
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<td></td>
<td>Behavior modification</td>
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<td></td>
<td>Pacing (energy conservation)</td>
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<td></td>
<td>Aids for activities of daily living (eg, 4 wheeled walker, reacher, commode)</td>
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<tr>
<td></td>
<td>Involvement of allied health team (physiotherapist, occupational therapist, respiratory therapist, nurse)</td>
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<tr>
<td></td>
<td>Maintain nadir SpO2 &gt;90% with exertion</td>
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<tr>
<td></td>
<td>Frequent titrations in clinic and home</td>
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<td></td>
<td>Patients and families have a pulse oximeter and learn how to self-manage their oxygen</td>
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<tr>
<td>5. Initiate and titrate oxygen</td>
<td>Opioids (example starting doses)</td>
</tr>
<tr>
<td></td>
<td>(if MDDS &gt;3/10 for rest, talking, eating): hydromorphone oral syrup 0.1-0.2 mg swallowed 3 times daily (before meals)</td>
</tr>
<tr>
<td></td>
<td>(if MDDS &gt;4-5/10 with exertion): hydromorphone oral syrup 0.2 mg buccally 10 minutes pre-activity</td>
</tr>
<tr>
<td></td>
<td>hydromorphone oral syrup 0.2 mg buccally every 10 minutes as needed</td>
</tr>
<tr>
<td></td>
<td>Consider use of adjuvant sublingual lorazepam for anxiety and methotrimeprazine for agitation that may accompany crisis dyspnea</td>
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</tbody>
</table>

### Case Series

#### Opioid Initiation Within the Last 6 Months of Life

Case 1 was a 72 year old male who presented with 1 year of dyspnea on exertion (Medical Research Council dyspnea scale 3/5) and mild non-productive cough. Imaging suggested usual interstitial pneumonia (UIP), and pulmonary function tests were consistent with a restrictive pattern. He was unable to tolerate antifibrotic therapies (pirfenidone and nintedanib). Energy conservation and pacing were taught, and within 4 months oxygen was initiated with flows of 3 LPM at rest and 5-10 LPM with exertion. A month later, an episode of crisis dyspnea and persistent dry cough prompted a hospital admission for treatment of an acute exacerbation of IPF. His MDDS scores were >3/10 at rest and >5-7/10 with exertion. His goals were to better self-manage his breathlessness, independently perform activities of daily living (ADLs) without dyspnea crisis, spend time comfortably with family and avoid further hospitalizations. He also wished for one last road trip to visit family in a neighboring city. Non-pharmacological approaches to dyspnea management were reviewed (Table 1). His oxygen flows were increased to 12 LPM at rest and 15 LPM with
exertion. Based on his MDDS scores, he was started on hydromorphone oral syrup: swallowed 3 times daily before meals for baseline breathlessness; via buccal route 5-10 minutes pre-activity for incident dyspnea; and via buccal route every 10 minutes until settled for crisis dyspnea. He was advised to have at least 20 pre-filled oral syringes available at all times for quick access. With increased oxygen flows and hydromorphone, his cough dissipated and he had no further episodes of crisis dyspnea or hospital admissions. Following discharge, he enjoyed the family road trip he had envisioned on account of effective dyspnea self-management. Within 1 week of returning home, he experienced a dyspnea crisis from breakdown of one of his 2 oxygen concentrators. He stayed home but needed increased oxygen flow rates of 24 LPM via both mask and nasal cannula, with even higher flows to facilitate self-toileting and ambulation. His hydromorphone dose was increased to better meet his needs, but was too large a volume using the oral syrup formulation to hold comfortably in his cheek. It was therefore changed to the more concentrated injectable formulation (10 mg/mL, used off-label) for a higher dose with smaller volume used buccally. Sublingual lorazepam as needed was prescribed for anxiety, along with buccal methotrimprazine as needed for crisis agitation. The night before he died, he was still dressing, toileting and bathing himself, and interacting with family. He was homebound only for the last week of life.

**Opioid Use Starting 1 Year Prior to Death**

Case 2 was a 71 year old male diagnosed with IPF in 2013 and intolerant of initial antifibrotic therapy. Three years later, he was referred to our MDC ILD clinic. His main concerns were cough and dyspnea with exertion (MRC 3/5). He was on oxygen at 3 LPM but desaturated well below 90% with walking, therefore was advised to increase oxygen flows with exertion to maintain nadir exertional SpO2 >= 90%, and was started on another antifibrotic agent. Four months later, he reported improved dyspnea during light exertion and ADLs, but increased dyspnea during exercise (MDDS 5/10) and mild baseline dyspnea (MDDS 0-3/10). Therefore, 13 months after his first visit he was started on buccal hydromorphone oral syrup 0.1 mg 10 minutes prior to light activity, and a higher dose (0.2 mg) prior to more intense activity. For crisis breathlessness, he was advised to take hydromorphone oral syrup every 10 minutes via buccal route until symptoms were controlled. Hydromorphone was not prescribed around the clock because baseline dyspnea scores at rest, with talking and eating were all low.

Over the next several months, his dyspnea was better controlled with 10 buccal doses per day of 0.1 mg per dose pre-activity, but his lung function continued to deteriorate. With further progression of IPF, he eventually required increased oxygen flow rates of 20 LPM at rest and 28 LPM with activity, higher doses of buccal hydromorphone oral syrup, and initiation of hydromorphone oral syrup swallowed 4 times daily (at mealtimes and bedtime) to reduce his worsening baseline dyspnea scores. Despite advancing disease, he reported a good quality of life, being able to self-manage dyspnea which allowed him to engage in social events in and outside his house. He remained independent with ADLs and avoided hospitalizations. In line with his advance care planning, he passed away at home 2 years after first being seen at the MDC clinic. He was homebound for the last 6 months of his life, and had no hospitalizations in his last 10 months.

**Opioid Use Starting 5 Years Prior to Death**

Case 3 was an 83 year old male with IPF who presented to our clinic in November 2013 with 3 years of dyspnea on exertion (MRC 3/5). He was started on antifibrotic therapy. After 1 year of symptom stability, he had 3 admissions for worsening dyspnea, and then qualified for supplemental oxygen (2 LPM at rest, 4 LPM on exertion). In January 2015 he reported worsening dyspnea during ADLs and crisis dyspnea with coughing episodes; repeat pulmonary function tests confirmed deteriora-
Discussion

Dyspnea is a very unpleasant symptom that causes significant distress, readily over powering patients with IPF and their caregivers. Uncontrolled dyspnea is a major source of anger, frustration, helplessness, and hopelessness. Major guidelines suggest the use of low-dose opioids for management of dyspnea but do not specify an approach for IPF that includes the optimal route, dosage, and titration. We developed a novel scale, the MDDS, to facilitate rapid and comprehensive assessment of dyspnea with practical management implications for patients and clinicians (contact author MK for access). Development of the MDDS was based on the Edmonton Symptom Assessment Scale (ESAS), a validated and widely used 10-item battery for palliative cancer care that assesses 7 physical symptoms, 2 emotional symptoms, and overall well-being. The ESAS serves as a symptom screening tool to be integrated with a detailed clinical interview in order to better understand the patient’s perspective of their lived experience and guide interventions as well as the response to treatment. This tool lends itself well to adaptation for non-malignant palliative diagnoses, such as Parkinson’s disease. We adapted the ESAS and its numerical scale to focus specifically on dyspnea, giving the clinician more information about the circumstances when dyspnea occurs in a succinct, practical manner that can be easily integrated into clinic visits and taught to patients as a way for them to self-manage and adjust their behavior as needed. The MDDS consists of 9 items, which is shorter than other comprehensive dyspnea scales such as the London Chest Activity of Daily Living (15 items) or the University of California, San Diego Shortness of Breath Questionnaire (24 items). Although other dyspnea scales have been well tested and validated, they do not provide guidance on how to target treatment strategies for dyspnea. As the MDDS is yet to be validated, the minimal clinically important difference for improvement is not known at this time, though we would expect it to be similar to that of the ESAS (1 point). Ultimately, patient responses on the MDDS provide information essential to understanding the triggers, intensity and timing of dyspnea and the objective score is used in conjunction with a patient’s own subjective assessment of dyspnea control. This understanding then guides dyspnea management appropriate to the situation, including non-pharmacologic and pharmacologic approaches.

We prescribe opioids after addressing treatable and reversible contributors to dyspnea, including use of supplemental oxygen at appropriate flows to maintain nadir exertional saturation. Oral opioids that are swallowed come in formulations designed for management of pain which typically responds better to higher doses than required for dyspnea management. Pill formulations of opioids for swallowing are better-suited for managing baseline (or resting) dyspnea where a 30 minute onset of action and regular dosing through the day are more applicable; however, the lowest dose formulations of these pills are often still too potent for breathlessness management at the outset. In addition, these pills are not conducive to rapid self-management (within minutes) of incident (anticipated) or crisis (unanticipated) dyspnea because of a longer onset of action when swallowed. Therefore, we use hydromorphone oral syrup 1 mg/ml which can be readily drawn up in syringes in doses as low as 0.1-0.2 mg for initiation of opioids, and can be given orally (swallowed) for baseline dyspnea or buccally for management of incident and crisis dyspnea. Clinical trials of opiates via non-oral routes, including subcutaneous morphine and nebulized fentanyl, have been described in ILD. Subcutaneous morphine has an onset of action of at least 15 minutes and many patients and caregivers find use of needles intimidating and bothersome. Nebulized opioids are not practical for an active lifestyle and data on efficacy and safety is limited. Sublingual (or intranasal) fentanyl has been used for many years for incident and crisis management of pain, and more recently for dyspnea in COPD and congestive heart failure. The oromucosal route allows medication to be rapidly absorbed via the vascular rich epithelium of the cheek. The buccal route is a simple method for small dose-small volume drug delivery, and patients or caregivers can easily learn to prefill syringes and administer medication into the cheek for rapid and effective relief of dyspnea. The principle of drug delivery is similar to using sublingual nitroglycerin for angina. This method is conducive for use within or outside the home. We believe that the desired characteristics of a patient-centered opioid strategy for dyspnea include: 1) simple and easy for self-administration; 2) rapid onset of action—within minutes; 3) ability to prevent/decrease anticipated dyspnea; 4) easily titratable to match the intensity of dyspnea and disease progression; and 5) does not adversely impact alertness so that patients can remain active and engaged with their family and friends. Hence we adopted the use of the buccal route to manage anticipated incident and unanticipated crisis dyspnea. While hydromorphone oral syrup is not designed for the oromucosal route and the literature has not described good absorption, we inadvertently learned that it is indeed effective and absorbed. Its reduced bioavailability is supported by the need to reduce the dose in half when switching to the injectable formulation for administration via the buccal route. Although there are limited studies of buccal hydromorphone, especially when compared to sublingual fentanyl, we use hydromorphone oral syrup initially as it is able to be used in very low doses both orally (swallowed) and buccally. While buccal fentanyl could be used for incident and crisis dyspnea, with a fentanyl patch for baseline dyspnea (as we sometimes do), the duration of action of hydromorphone exceeds that of fentanyl, thus making it more conducive to managing the type of breathlessness in IPF where our patients tell us that there is too fast an offset of action with fentanyl. Another advantage to starting with hydromorphone oral syrup is the simplicity of using one formulation for all types of dyspnea—baseline, incident and crisis.

Though this case series is small, it is but a small sampling of the MDC clinic’s experience over 5 years with this regimen and demonstrates that buccal hydromorphone oral syrup is effective for reducing dyspnea intensity in patients with IPF. All the patients described were able to improve their function at home.
Table 2. Patient Goals, Opioid Doses, and Outcomes.

<table>
<thead>
<tr>
<th>Case</th>
<th>Patient goals</th>
<th>Initial doses of hydromorphone</th>
<th>Final doses of hydromorphone</th>
<th>Outcomes of buccal opioid self-management</th>
</tr>
</thead>
</table>
| 1    | Self-manage breathlessness  
Perform ADLs without dyspnea crisis  
Spend time comfortably with family and avoid further hospitalizations  
One last road trip to visit family | Baseline: 0.1 mg oral (swallowed) 3 times daily with meals  
Incident: 0.1 mg buccal 5-10 minutes pre-light activity, 0.2 mg buccal 5-10 minutes pre-more intense activity  
Crisis: 0.2 mg buccal every 10 minutes as needed | Baseline: 2 mg oral (swallowed) 4 times daily with meals and bedtime  
Incident: 2 mg buccal pre-activity  
Crisis: 2 mg buccal every 10 minutes as needed | More confidence with self-managing dyspnea  
Improved dyspnea, resolved cough  
Attended social events and traveled (road trip)  
No admissions after starting opioids  
Home death |
| 2    | Spend time with family  
Celebrate another Christmas  
See his grandchildren | Baseline: 0.1 mg oral (swallowed) 3 times daily with meals  
Incident: 0.1 mg buccal 5-10 minutes pre-light activity, 0.2 mg buccal 5-10 minutes pre-more intense activity  
Crisis: 0.2 mg buccal every 10 minutes as needed | Baseline: 1 mg oral (swallowed) 4 times daily with meals and bedtime  
Incident: 1.8 mg buccal pre-activity  
Crisis: 1.8 mg buccal every 10 minutes as needed | Improved dyspnea  
Improved cough  
Independent with ADLs  
No admissions after starting opioids  
Home death |
| 3    | Improve breathing  
Spend time with family for Christmas and see another round of birthdays and anniversaries  
Remain independent for ADLs | Baseline: 0.1 mg oral (swallowed) 3 times daily with meals  
Incident: 0.1-0.2 mg buccally 10 minutes pre-activity  
Crisis: 0.2 mg buccally every 10 minutes as needed | Baseline: 1.2 mg oral (swallowed) 4 times daily with meals and bedtime  
Incident: 1.2 mg buccally pre-activity  
Crisis: 1.2 mg buccally every 10 minutes as needed | More confidence with self-managing dyspnea  
Resolution of cough and chest pain  
Improved sleep  
No hospitalizations in last 5 years of life  
Home death |

with respect to ADLs, maintain dignity through personal self-care and meet their personal goals regarding how and where they spent their remaining time (Table 2). This is an unmet patient need reported by several qualitative studies in IPF. Dyspnea self-management allows patients to remain at home, empowering them and their caregivers with the knowledge and tools to prevent and self-manage severe symptoms without acute care utilization. Our patients have found that pre-filled oral syringes with hydromorphone syrup are easy to administer in the cheek. These strategies are easily escalated at the end of life for symptom management and help prevent dyspnea crises that would otherwise prompt emergency room visits and hospitalization. Buccal opioids, therefore, meet all the criteria for ideal dyspnea management as outlined above. The key to incident and rapid crisis management of dyspnea is having several prefilled syringes on hand for anytime use. We generally recommend that patients and caregivers have at least 20 prefilled syringes located on the person, for example, in a glasses case in a shirt pocket, fanny pack or armband for cell phones (as used by runners) for easy and rapid access, as hydromorphone syrup can be stored at room temperature.29 The convenience of using a 1 cc oral syringe allows the therapy to be rapidly scaled up with dyspnea progression or for end-of-life management at home.7,30,31

Some of the limitations of using hydromorphone syrup are that not all patients have the ability to prefill syringes themselves or have a caregiver do this for them, or can afford the pharmacy cost for prefilled oral syringes. Additionally, admission to hospital or hospice beds poses a challenge to patients who become accustomed to effectively self-managing their breathlessness as most facilities do not allow patients to keep prefilled syringes of a controlled substance at their bedside. Some patients may have cognitive impairment which prevents them from taking responsibility for self-management of their breathlessness. If the patient has a caregiver who lives with them and is willing to help supervise and manage symptoms, then the caregiver can be taught how to pre-fill and administer syringes. Close monitoring is essential to ensure success and safety.

Our preliminary findings suggest that the use of buccal hydromorphone oral syrup is easy, feasible and effective across the spectrum of IPF. The MDDS scale facilitates initiation and titration of buccal hydromorphone for rapid self-management of incident and crisis dyspnea. This approach empowers patients and families to live a meaningful life until death by improving functional ability, HrQoL, meeting realistic patient goals and avoiding hospitalizations. Prospective studies can
confirm our findings and help build the much needed evidence base for effective therapies for dyspnea relief in IPF.

**Authors’ Note**
Dr. Janice Richman-Eisenstat and Dr. Meena Kalluri are also affiliated to Alberta Health Services, Edmonton, Alberta, Canada.

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