Opioids for Refractory Dyspnea in Patients with Advanced Chronic Obstructive Pulmonary Disease: A clinical trial

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Abstract

Background: Dyspnea that is refractory to conventional treatments affects up to 50% of patients with advanced COPD. While professional societies recommend opioids in this setting, evidence supporting their use over months is limited. We conducted a multi-centre mixed-methods study to understand patients' experiences when opioids are added to optimized conventional treatments for advanced COPD.

Methods: 44 patients participated in this 6-month study. After baseline assessments, morphine syrup (initially 0.5 mg BID) was titrated slowly based on weekly symptom assessments. We conducted semi-structured interviews and collected contemporaneous measures of health-related quality of life (HRQoL), dyspnea intensity, anxiety, depression, global ratings of opioid "helpfulness" and opioid side effects before, at 2 months, and 4-6 months after initiating opioids.

Results/Findings: Of 44 patients, median age 74, range 51-89 years, 32 (73%) completed the trial with 27/30 (90%) reporting opioids as very (43%) or somewhat (47%) helpful. Beyond an overall positive opioid experience, 3 main themes emerged from qualitative findings: 1) small gains beget big impact; 2) realigning expectations; 3) "try it, there's nothing to lose". HRQoL (Chronic Respiratory Questionnaire, CRQ median (IQR) 3.5 (2.8-4.0) vs 4.2 (3.6-4.8), $p<0.0001$), dyspnea intensity (Numerical Rating Scale 7.0 (5.0-8.0) vs 5.0 (4.0-6.0), $p=0.024$; CRQ-Dyspnea domain 2.8 (2.3-3.6) vs 3.9 (2.8-4.5), $p=0.004$) improved significantly at 6 months. Side effects were minimal for most patients.

Interpretation: Opioids are a helpful and acceptable intervention for refractory dyspnea in advanced COPD. Many patients experience sustained benefits over months, supporting recent professional society recommendations to consider opioids in this setting.

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Chronic Obstructive Pulmonary Disease (COPD) will be the 3rd leading cause of death globally by 2020[1]. Recent Canadian data suggests that about one in four adults ≥ age 35 years can expect to develop COPD[2]. Dyspnea is the predominant symptom and in advanced COPD, up to 50% of patients experience dyspnea that is refractory to conventional treatment[3]. Dyspnea can be persistent, episodic or both, and dyspnea 'crises' often trigger intense anxiety, fear, panic, and feelings of helplessness that can overwhelm patients' and caregivers' abilities to cope[4].

Twenty years have passed since morphine was found to be associated with a reduction in dyspnea in patients with COPD [5], and despite the systematic review of a decade ago[6] experience with using opioids in this context remains limited. Subsequent evidence has focused on or has been extrapolated from short-term effects over hours[7, 8] or days[9]. Longer-term clinical use (months) has received relatively little attention or support until recently[10, 11]. The current dearth of quality evidence relating to the longer-term effects of opioids for patients with advanced COPD prompted this study.

Building on our previous research in this area[12, 13], we designed a multi-centre mixed-methods study to: 1) further understand the experiences of patients living with advanced COPD and suffering from refractory dyspnea when opioids were added to optimized conventional treatments, 2) explore the longer-term effect of opioid therapy (4-6 months) on dyspnea, health-related quality of life (HRQoL), anxiety, depression, and 3) determine why patients chose to dis/continue opioids.

Method

Design/Approach

This multi-centre, prospective, longitudinal, observational interventional study had parallel qualitative and quantitative design features. It was approved by Health Canada and

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received Research Ethics approval from each study site (Capital District Health Authority, Halifax; Horizon Health Network, Saint John; University of Saskatchewan, Saskatoon).

Setting

The study was conducted in 3 centers that included urban and rural settings in Nova Scotia, New Brunswick, and Saskatchewan.

Recruitment

While a formal sample size calculation was not appropriate for this study design, we considered effect size, placebo effect rate, and potential attrition rates/loss to follow up. As such, an initial recruitment of approximately 30-45 patients was projected as sufficient for our study objectives. Potential patients were those who had a confirmed diagnosis of advanced COPD, (Medical Research Council (MRC) 4-5) and who were experiencing refractory dyspnea despite optimal conventional treatment as defined by 2008 Canadian Thoracic Society (CTS) COPD guidelines[14]. We excluded patients with a documented overlap syndrome (additional obstructive sleep apnea or hypoventilation (see Appendix 1 for complete study inclusion/exclusion criteria). For any eligible patient who had experienced an acute exacerbation of COPD prior to study intervention, the initiation of opioids was deferred for at least 4 weeks and until patients felt they were back to their baseline. Patients' primary clinicians referred potential and interested participants to the study research coordinator who provided additional details by phone and/or in writing. Consent forms were mailed to some participants to review in advance, however most preferred to have the study coordinator review the informed consent document in person. During

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the first visit to confirm eligibility or exclusion, study investigators addressed any fears or concerns patients had about opioids and how they would be administered.

Sampling for Qualitative Component of Study

We used criterion sampling to enroll a homogeneous sample of participants with advanced COPD familiar with the phenomenon of interest (living with intolerable dyspnea despite being on optimized conventional COPD treatment). This ensured data sufficiently rich to allow insight into such patients' experiences with opioid therapy.

Intervention

Local investigators who prescribed the opioids assessed potential benefits and harms as in any clinical encounter (e.g., lower doses with renal impairment, low body mass index). Unless contraindicated, patients were started on oral immediate-release morphine sulfate liquid suspension as per the schedule in Table 1. We intentionally chose a low starting dose and wide dosing interval for the first 2-4 days of treatment in order to minimize the likelihood of early opioid related side effects that might increase non-compliance. We chose this approach to help gain patients' trust, which was important enough to justify a slight delay of any therapeutic effect. Since patients were most likely to experience dyspnea when most active (during waking hours), we gradually shortened the dosing interval to q4h while awake, aiming to provide adequate levels of opioid for 16 of 24 hours.

Patients were given prescriptions for an initial 2-week supply of morphine liquid suspension. All patients received a diary to record opioid doses/frequency, and to log reasons for missed doses, extra doses and treatment related side effects. As a secondary check on

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compliance, we asked patients to have study medication available during investigators' assessments in the home/clinic. We provided patients, their family caregivers, and family practitioners (for interest) with our opioid titration guide (Table 1) and monitored closely through telephone contact during the first two weeks of therapy. At each phone contact, patients rated the "tolerability" of their dyspnea on a 5-point Likert scale. For those wishing to continue with the trial, opioids were titrated upward gradually as required to achieve tolerable levels of dyspnea.

Initiation of opioids was slow over week 1 and dose stabilization occurred at weekly intervals over 4 weeks and as per our previous recommendations[15]. Once a stable effective dose was established most transitioned to a daily or twice daily sustained-release preparation, with additional immediate-release preparations for episodic increases in dyspnea. If patients reported that side effects exceeded benefit, doses were reduced, other opioid preparations were considered, or opioids were weaned or discontinued. We also provided written advice regarding regular use of stool softeners and stimulant laxatives to prevent and treat opioid-induced constipation (Appendix 2). For patients with persistent or intolerable side effects, an equipotent dose of hydromorphone (conversion factor of 1mg oral hydromorphone = 5mg oral morphine) was offered.

Table 1: Opioid Dosing and Titration Schedule

Data Collection

After obtaining informed consent, we collected demographic data (Appendix 3) and conducted semi-structured one-on-one interviews with all participants. Research assistants with experience in qualitative interviewing explored participants' experiences of living with COPD

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and refractory dyspnea along with attitudes to opioid use. Interview guides (Appendix 4) were developed through an iterative process based on themes identified in our previous research, literature reviews conducted in preparation for these studies, and testing of the interview guide in pilot studies[12, 13]. Prompts were rarely needed as study participants readily discussed their experiences and concerns.

Patients completed validated quantitative assessments for dyspnea severity[16, 17], functional status[18], anxiety/ depression[19], and health-related quality of life (HRQoL)[20] before and during opioid treatment (Table 2). Additionally, they rated the global "helpfulness" of opioids on a 5-point Likert scale (1= not helpful at all and 5 = very helpful); whether, when balancing benefits and side effects, they wanted to continue opioid therapy (Yes/No); and the reasons for their choice in terms of changes in dyspnea, quality of life, and/or side effects[21]. Patients completed quantitative assessments after their qualitative interviews, or if fatigued, completed and returned them to the study coordinator within a few days.

Table 2: Timelines

Analysis of Quantitative and Qualitative Data

We used median (med) and inter-quartile range (IQR) to describe continuous data at single time points and the Sign test to assess for significance of differences between baseline and 4-6 month scores. Although most data were normally distributed, for consistency we used non-parametric analysis throughout in light of the small sample size.

Following verbatim transcription of digitally audio-recorded interviews, our qualitative

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research assistants analyzed the data using "interpretive description" to capture practice-relevant particularities of individual experiences as well as broader commonalities across those experiences[22]. We have presented the details of our analytic approach elsewhere[12]. In brief, we began by describing the phenomenon of interest (patient experiences with opioid treatment for dyspnea in advanced COPD). Through a process of thematic coding and analysis we interpreted possible meanings of the described phenomena from a clinical perspective. NVivo 7.0 ™ and Atlas.ti software programs were used for data management.

Results

Between March 2010 and November 2011, 47 patients were enrolled, of whom 45 patients (26 females, 19 males) with median (range) age of 74 (51-89) years provided baseline data among the three study centres (n= 31 in NS; n=8 in NB; n=6 in SK). At enrollment, most patients (37/45, 82%) had an MRC dyspnea scale of 5 (i.e., they were too short of breath to leave their homes or breathless when dressing or undressing). The remaining 8/45 (18%) had an MRC scale of 4 but met additional enrollment criteria indicating disease severity (see Appendix 1). Most (58%) had a Palliative Performance Scale of ≤60%. Additional demographic data are presented in Table 3. Of 45 patients providing baseline data, 44 began opioids in addition to conventional treatment, and 32 (73%) completed the study. We describe attrition and drop outs in Box 1.

Table 3: Baseline Demographic Data

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Box 1: Attrition

From the enrollment cohort of 47, three subjects withdrew pre-intervention. One withdrawal was due to a motor vehicle accident days before planned commencement of opioids; this patient contributed to the baseline data set of 45 patients. Two other patients did not contribute to the baseline dataset - one withdrew after changing her mind about participation over several weeks, the other due to other intervening and persisting new health concerns.

Three patients died during the course of the trial - two between 2 weeks and 2 months and the third between 2 months and 4-6 months (see Figure 1): one died at home (cause of death unknown however he had made a routine call to his respirologist 24 hours earlier), and two died in hospital (one after an admission for severe respiratory failure, the other with severe back pain). None of these deaths were unexpected nor attributed to use of opioids. For both patients who were hospitalized, their attending physicians either continued or increased their opioid dosing to provide effective palliation in terminal stages.

Nine patients withdrew from the trial (MRC 5 n=6, MRC 4 n=3), one after a single dose citing feeling 'squirly', another at Day 5 with complaints of feeling 'worse than he had in 40 years' (this patient was subsequently and successfully treated with an alternative opioid for his dyspnea but chose to withdraw). A third patient was admitted to hospital with severe constipation after a misunderstanding about speed of dose escalation; her opioids were discontinued and not restarted. The other 3 patients who withdrew between 2 weeks and 2 months or between 2 months and 4-6 months (n=3) did so because they gained no overall benefit to justify continued use.

Patients who completed the trial (n=32) were taking a sustained-release preparation (10 mg daily (n=12, 38%) or 15mg daily (n=7, 22%)) as their primary opioid at trial endpoint. Only one (3%) had reached a daily dose of 20 mg while others remained on immediate-release Morphine (n=9, 28%, average daily dose 5.4mg) or hydromorphone syrup (n=3, 9%).

Figure 1: Flow of patients through the trial.

Lived Experiences and Thoughts about Taking Opioids

Most patients with advanced COPD who completed the trial described the experience of taking opioids as positive in terms of perceived benefits outweighing burdens (Box 2).

Box 2: Positive Assessment
It helped me and I have no side effects that I know of from it. So it didn't do me any harm and… [it helped] me more than it hindered me cause as far as trying to think of anything it did negative, I can't. There's nothing negative there at all, and everything that helped me I think it was positive from that. Because since I started taking that I felt way better… If somebody wanted to get on it, put them on it. It's not going to hurt them, no. (NS25-3)
I find like I'm feeling 100% better than I did before. And anybody they want to give that to, they should give it to them, anybody that wants to take it, should take it. Cause it is good. (NS010-3)
I think you guys have done wonderful things for this old fella. Thank you for going to the trouble of maybe at least giving him a little better quality. (NB02-3)

Three themes were identified within the "benefits over burdens" experience: 1) Small gains/big impact; 2) ongoing realignment of expectations; and 3) Try it!

1. Small gains/big impact (Box 3)

Baseline interviews indicated participants' desire to live as well as possible for as long as possible but also their modest hopes in this regard. Their expectations indicated a sense of resignation, resilience, and hope for small improvements or slowing deterioration. On opioids, small gains related to shortness of breath and accompanying anxiety significantly impacted QoL in terms of improved activity level, mood, relationships, and/or independence. Such changes were welcomed as minor miracles in the face of what was felt to be inexorable illness progression -- "small gains/big impact."

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Box 3: Small gains/big impact
It seems that I'm always climbing up hill, and I get sort of tired of climbing up that hill or trying to get out of that barrel or whatever I'm in….It's maybe hard for somebody that isn't the way I am to understand or feel …. you're grasping for any little thing that comes along and this morphine I guess it's been the best little thing that I've grasped for, for quite a while and even that little bit of help is a little bit of help, not down but rather up. (SK02-2)
It's made quite a difference for me. I wish I had heard about it sooner. It makes doing my chores a little more bearable and you know at this stage for me it's all about quality of life and if I don't have much quality of life, then what's the point of being her. So I think the morphine helps, it helps me to be able to enjoy things like, even taking a bath, I still enjoy my bath. And just walking and stuff, I can walk a little bit further without having to rest and when I do have to rest, I can get my breath back quicker and just different things like that so. You put those little things all together and it's a big thing, right? (NS024-3)
Well I've been able to maintain it, I guess my quality of life hasn't deteriorated over the last six months. I've been able to maintain the same level. I'm happy with that. (NB06-3)

a) *Improvements: benefit over burden (Box 4)*

Individually, patients referred to varying types and degrees of improvement that contributed to better QoL. The most common improvements related to breathing (less of a struggle, shortness of breath less severe, less need for rescue medication), activity/mobility (quicker recovery, improved mobility), and anxiety (calmer, less anxious and fearful). Some patients noticed improvements in mood (less irritable, more positive outlook), depression, hope, relationships with family or friends, and/or sleep. Many noted fewer visits to their doctor and the emergency department. Several felt opioids had extended their lives and one said it had helped avoid long-term care.

Box 4: Improvements
<u>Breathing</u>
It just takes the edge off that ragged breathing that I've had. It's made quite a difference for me. ...when I do have to rest, I can get my breath back quicker. (NS024-3)
My breathing has changed a bit, not 100% but it's suitable for me that I get around better. And as long as I stay on the right hours, if I miss one [dose]*, an hour later or something you can tell the difference... Otherwise it's been good for my breathing. (NS030-2)*
Probably the best thing I've noticed it [morphine] *has changed is when I get short of breath I'm*

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not gasping as much as I used to. (SK05-3)

Activity/Mobility

I've been cleaning out the kitchen, cleaning out the cupboards and things like that, take my time ... but I've noticed a big difference in things like that. (NB01-3)

Oh my god. Well I move around easier. I find that I'm more hopeful, I have a drive to get out of bed and do things and I see to have more energy to do things. (NS24-3)

Independence

I can do more things, without getting breathless, like more things for myself rather than depending on [spouse] *all the time. That's a big thing for me. (SK04-2)*

Mood/Relationships

I've noticed that I don't get quite so uptight ... as I used to, I don't like to nag, to me it's being negative and I find now that I can respond where it's not instant fury or instant feeling sorry for myself. I still get that way to a certain point sometimes, depending on what's happening, what's being said but... so it's keeping me calmer I guess, or on a more even keel. (SK04-2)

I'm not so sure because I mean quality of life for me is with the little ones and with my family and that has continued and yes I suppose because I've felt better so therefore I was able to enjoy them more and participate more even though it's been little you know, so yes I believe it has improved my quality of life. (NS007-3)

Perceptions of Life Expectancy, Physician Visits, and Symptoms

Ah, they [fears] *may have improved some,...since it's a terminal illness that I have, maybe we put the termination date off into the future somewhat. And we've extended my life. (NB06-3)*

The pain has gotten better, I had terrible pain in my arms and my shoulders and that's got significantly better and my breathing has gotten a lot better, a lot easier when I take morphine and whereas before I was using my aerosols like three or four times a day, and going down to [ED] *two or three times a week usually because of poor breathing and I haven't had that since I've been on the morphine hardly at all. (NS010-3)*

b) *Other benefits: support and trust/desire to continue*

Beside small gains in QoL, many participants appreciated the support they received from and trust they developed in the study team. The number of participants who chose to continue with opioids at the conclusion of the study was taken as a further indication of their positive sense of the overall experience (Box 5).

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Box 5: Support and trust/Desire to continue
Support and trust
No I can't think that you people could have done any more than you have for me. You know you were right there, [study RRT] *was always there at the end of the phone if we needed her. (NB01-3)*
It's perfect as far as the staff... the staff have been very helpful. I've got the calling card right here for [study RRT]*, any time I want her. (NB02-3)*
Desire to continue
I told them I'd keep it up. I've already been talking to my family doctor and he's willing to prescribe and everything for me. (NB02-3)
It [experience taking opioids] *has improved since and I noticed a difference without it…If it's possible to continue with the morphine after the study is done, I think I would like to go with that. (SK04-2)*

2. Realigning expectations: hope/disappointment

Despite early positive assessment and modest hopes, the opioid experience necessitated ongoing realignment of expectations for most patients as benefits and burdens ebbed and flowed.

a) *Disappointment*

Early improvement was often followed by a plateau or diminution in effectiveness, engendering some disappointment and concern (Box 6). A few experienced inconsistent effectiveness, leaving them unsure about whether or not to continue. A small number reported insufficient or no improvement along with a burden of side effects and/or dosing difficulties leaving them disappointed and sad.

Box 6: Disappointment/inconsistent effects
The shortness of breath got better for a while but then it went right back to what it was before I started taking the morphine... It gradually got better from the time I started up until about three weeks ago. (NS001-3)
I am kind of disappointed. I thought maybe it would be better for that trip. But it was about the same as the pre-morphine period. (NS28-2)
One day it will help me and the next day I find no difference in it ...some days I can't tell you know like if it's working or not. (NS029-3)

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So ah, all in all I didn't feel that I was getting anything from it so it was just another burden. I was so hopeful. (NS002-3)

b) *Burden exceeded benefit for a few*

For the few patients who rated the opioid trial as negative or neutral overall, the negative aspects of side effects and opioid dosing outweighed any impact on symptoms, QoL and resulted in more burden than benefit (Box 7).

Box 7: Negative effects, dosing issues

I couldn't feel anything at all in the line of difference ...yeah it was another burden sort of thing ...between the time elements and the constipation. (NS002-3)

When I first started taking the morphine I had a lot of stomach problems as well, I had an enormous amount of gas and upset stomach and queasiness and so on…. That disappeared but was replaced with the constipation problem. (NB004-2)

I know the pills are far, far easier than the other [syrup]*... that's time consuming like if you're going anywhere or [doing] anything. You've got to dig this out and you know what have you, but anyway so the pills do, I think they go for twelve hours don't they? They must cause you only take them once a day, 24 hours I meant to say yeah. (NS029-3)*

The liquid is a pain to take, especially if you're out or something. This way [long-acting form] *if you're going out I throw a tablet or a capsule in my pocket and I pop it. (SK002-3)*

i) Adverse side effects

Gastrointestinal symptoms, primarily constipation, were the most frequent and troubling side effects reported. A few patients complained of nausea, vomiting, bloating, cramping, and loss of appetite, most of which resolved over time and as constipation was better controlled. Other reported side effects included sleepiness, itching, dry mouth, sweating, dizziness, and/or skin changes, but the experience of one patient accounted for most of these.

ii) Difficulties with opioid dosing

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Difficulties identified by patients related more often to the short-acting syrup used to initiate the opioid intervention - including taste, messiness and difficulty of drawing up a dose, frequency of dosing, difficulty transporting and taking it when away from home (Box 7). Most of those who commented on the dosing preferred the longer-acting pill form that could be taken once a day after they reached a dose of 10 mg per day or more.

c) *Uncertainty*

Initially many had significant concerns, primarily related to risk of addiction, sedation, and associations with end-of-life, cancer, and pain. They also wondered about dose changes, dose effects, the future, and their desire to continue with opioids beyond the study.

Box 8: Uncertainty/the future
I'm not as afraid of it as I was. You know I was afraid because you hear "morphine" and you think "addiction." (SK004-2)
I immediately said to her [interviewer], I said I'm not going to become an addict am I? (NB01-1)
Well at first I thought it [morphine] was just at the end of life and I didn't want to start it because I thought I didn't need it for, you know, for the end of life. (NS07-1)
[I: when the doctor came and saw you at home and talked to you about the morphine, what was your first thought when she talked to you about that?] Cancer. I told Dr. [name]. I was in the hospital. (NB05-1)
I don't know where we go from there [15 mg]--is there a higher dose or a lower dose? (NB006-2)
Where did the 15 [mg] come from, when the dart hit the board, that 15, when they threw the dart it landed on the 15? How did they say mine should be 15?(NS28-2)
Now maybe if I took 10 mg a day or something, maybe then I would, if I were to stop, do I stop just, or do I have to taper? (SK002-3)
Yeah, my point is maybe if I slid down to 10, all these other side effects would disappear or go to nothing. You know what I'm saying?(NS28-2)
That's a good question, stay on it or not. Do you think I should have stayed on longer? (SK006-3)

3. Try it!

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Regardless of their overall assessment of the experience, most appreciated having had the chance to try opioid therapy. Overwhelmingly, their advice to others in similar situations was "try it, you have nothing to lose." Implicit in the words "try it" was their recognition that there are no guarantees of effectiveness. Most seemed to feel that at their stage of illness, any option that might improve QoL, even marginally and for a short time, was worth a try. Having completed the trial they were more confident than ever of this advice, even those for whom the experience was less than positive.

Box 9: Try it

I would say anything that can help. If it will help me, I decided I'd give it a go... to try to see if it will help me get more breath. It would be easier for me to live, in other words, if it's possible, so that's it. (NS06-1)

Do it. Just do it. Just do it, if you've got COPD do it. Dare to try. I don't know, maybe it doesn't work for everybody, but you don't know unless you try it right. I know it worked for me and I'm glad I tried it. (NS24-3)

No, but I think that they shouldn't hesitate right off the bat. It's a program laid out that there's hope, that, it improved my day-to-day life and they should just latch on to that, grab hold. Anything is better than nothing when it comes to breathing. (NS28-2)

I've realized a long time ago, I'm not going to get better. In fact, it's going to be the other way around so for people that are in my position… if taking morphine helps you just that little bit you know so that it gives you a positive attitude or positive little bit, I'd say hey go for it. (SK002-2)

To me, every little improvement is a big thing because it's, I don't know how to put it into words, if, you know if you're swimming and there's nothing around to hold you up and suddenly there's a plastic gallon container floating around there and you can grab on to that and that's keeping you afloat, well so maybe morphine is that for me. Is that a good analogy? (SK002-3)

In summary, for most participants who completed the study, the experience was positive in terms of "small gains making a big difference." Disappointment due to negative side effects, dosing difficulties, and waning, inconsistent or inadequate effectiveness necessitated a realignment of expectations for some despite their initial modest hopes. For a few, the gains were

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not sufficient to outweigh these negatives, which resulted in an overall negative or neutral assessment of their opioid experience. Despite this the vast majority appreciated the opportunity to "try it" and strongly endorsed others in this illness context to do likewise, the implication being--"you have nothing to lose but potentially something good to gain."

Quantitative Data

At 4-6 months, of the original cohort (n=44) who took an opioid for refractory dyspnea, 29/44 (66%) had found it helpful. The proportions of patients finding their opioid therapy helpful (or not) at 2 weeks, 2 months and 4-6 months are shown in Figure 2.

Figure 2: Global ratings of "helpfulness" of opioids on 5-point Likert scale

Quantitative measures support the qualitative findings (Table 4). Early improvements in dyspnea intensity (both NRS and CRQ-D, Figures 3, 4a) and in HRQoL (CRQ, Figure 4b) were maintained through the next months (Table 4). The improvement in a more global measure of QoL (McGill - QOLLTI–P) was of borderline significance (p=0.053).

Table 4: Changes in Quantitative Measures for Patients from Baseline to 6 months

Figure 3: Box plot of NRS from patients completing the study (n=31), baseline to study endpoint

Figure 4a: Box plot of CRQ-D from patients completing the study (n=31), baseline to study endpoint

Figure 4b: Box plot of CRQ from patients completing the study (n=31), baseline to study endpoint

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Side Effects: Of 10 key side effects, nine did not change from baseline to 6 months (Table 5). Scores for dry mouth fell. There were no issues of compliance or abuse, and no prescriptions needed to be filled ahead of schedule.

Table 5: Patient Self-reported Side Effects of Opioids

The study participants in NS and NB who reached 2 months (n=32) and then 4-6 months (n=29) provided responses regarding choices (and strength of choices) to continue (or not) with opioids in terms of relief from dyspnea or improvements in QoL, or both. We summarize these data in Table 6a. These choices were informed by patients' assessments of the opioid benefits and side effects balance as summarized in Table 6b.

Table 6a: Reasons to Continue (or not) with Opioids

Table 6b: Balancing Benefits and Side Effects of Opioids

Clinical Issues

The mortality rate of 7% (3/44) was lower than expected given participants' disease severity and projections from other studies[23]. We anticipated acute exacerbations of COPD (AECOPD) and beyond the two 'terminal' admissions (Box 1), the remaining 17 AECOPD admissions (n=11 patients, duration 3-17 days) ran expected clinical courses (early BiPAP for some as in admissions pre-dating opioids). Mostly, opioid doses were unchanged, in a few cases were weaned slightly for a few days, or in two cases increased. All patients were discharged on pre-admission doses.

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Interpretation

Treatment with opioids proved to be helpful for 66% of patients whose dyspnea was refractory to conventional therapy for COPD. Beneficial effects were achieved early, and for most patients were sustained over several months. Some improvements to QoL were dramatic, and in general patients indicated that small gains had a big impact on breathing, activity levels, and mood. Some realignment of expectations was still necessary and there was a palpable disappointment for the few who gained no benefit. For both HRQoL (CRQ) and dyspnea (CRQ-dyspnea domain and NRS) the change (vs baseline) at 4-6 months well exceeded the minimal clinically important difference established for these tools[24, 25]. Side effects were also minimal for most patients who felt that some side effects were an acceptable trade-off for the improvements they experienced in their dyspnea and/or HRQoL.

Comparison with Other Studies

Two other studies have reported effects of opioids over weeks to months. An early 6-week crossover study from New Zealand rapidly moved a cohort of 16 patients with COPD from a starting dose of 10 mg daily to a potential daily dose of sustained-release morphine of 40 mg at two weeks[26]. There was no change in CRQ in the treatment versus placebo group and almost all patients experienced adverse effects. While 25% of patients in this study chose to continue with morphine in an open-label phase at three months, the authors concluded they would not recommend morphine as a treatment for most patients with severe breathlessness caused by COPD[26]. More recently, in a dose increment and pharmacovigilance study of 83 patients with refractory dyspnea in Australia (n=45 due to COPD)[10], sustained-release morphine was initiated at 10mg daily, increasing to 20 or 30 mg if not effective. No benefit was seen beyond 20mg

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daily. There were no cases of respiratory depression during a mean follow up of 3 months and at 3 months benefit from opioids had been maintained for 33% overall[10], though its not possible to determine the proportion of patients with COPD (versus other etiologies) who found benefit.

Our study builds on previous findings by using a more individualized approach to initiation and titration of a short-acting opioid preparation and evaluating both quantitative and qualitative measures of dyspnea and quality of life QoL over a longer follow-up period in a cohort of patients with refractory dyspnea exclusively due to advanced COPD. Few patients chose to withdraw from our trial and at 4-6 months 66% of patients favored continuing treatment. In contrast to previous studies, our qualitative evaluation provided practical insights into the patient experience of dyspnea that small but statistically significant changes in measurable objective variables cannot provide.

Limitations

Limitations of this study include a potential sampling bias; most patients were enrolled in the primary centre where the principal investigator and team had significant experience with using opioids for dyspnea in this population. A potential placebo effect may be operant, which we considered in our sample calculation, but we also anticipated that patients' fears of opioids would sufficiently counteract this. The small sample size limits the generalizability of our findings; however, generalizability to all advanced COPD patients was not our intent, as per our individualized pharmacotherapeutic approach. Finally, given the extent of the unknown factors related to prescribing opioids for refractory dyspnea (such as opioid formulation, optimal initial dosing and titration schedules[15, 25], and outcomes meaningful to patients[27]), we felt it premature to conduct a randomized controlled trial (RCT) to quantify the effect of such an intervention.

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Nevertheless our study adds considerably to the current evidence base and should inform sample size calculations and design of future RCTs.

Strengths

Our study has a number of strengths. We used a mixed-methods approach to understand the complex phenomenon of living with refractory dyspnea of advanced COPD, before and after introducing opioids, consistent with calls for this approach[25]. We conducted extensive qualitative interviews and administered several questionnaires to provide a comprehensive assessment of this experience and used both unidimensional (NRS) and multidimensional quantitative assessments of dyspnea (CRQ) as recently recommended[16]. We assessed participants over months (compared to other studies to date of shorter durations), thereby substantiating the safety and efficacy of this treatment option for refractory dyspnea[10]. Only 9/44 patients (20%) withdrew, 7/9 beyond two weeks of treatment. We had surprisingly high completion rates (80-90%) for our questionnaires considering the advanced nature of disease of study participants. Finally, patients were enrolled, and opioids titrated, based primarily on symptom severity and not on considerations of the presence or absence of chronic respiratory failure. This provides confidence that the initiation, titration, and maintenance of opioid therapy in patients with advanced respiratory disease can be done safely without invasive monitoring.

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Lessons Learned: We summarize several lessons learned in Box 10.

Box 10: Lessons Learned

1. **Gaining trust**. Many patients assume that morphine is used when people are dying. When patients understood instead that our intent was to use opioids to potentially help them to *live* better, they were more willing to consider a trial of opioids. A simple strategy that worked for many was to discuss how our starting dose of morphine related to (and was much lower than) the dose equivalent in a tablet of Tylenol 3, a medication that was more familiar and less intimidating to many.

2. **Small gains matter.** Patients very much embody their own advice "try it--you have nothing to lose." Many do not have great or unrealistic hopes going into such trials and thus small gains become quite significant given the poor QoL that often predates their opioid experience.

3. **Anticipate disappointment.** Despite, or perhaps because of, their rather meager hopes, disappointment looms larger and seems more devastating in these circumstances. Communication is key and requires ongoing monitoring of, listening for, and responding to questions, concerns, and change, both positive and negative.

4. **Each patient was in reality a case of N=1**. Each had a unique baseline situation; each had a unique response regarding dose effects initially and over time, side effects, development of tolerance, etc. There is no "one size fits all" approach when using opioids for refractory dyspnea.

5. **Inadequate treatment of constipation**. This was a source of significant suffering for some patients in the trial. Being willing to stay on top of side effects and work to find appropriate, timely answers is an important part of sustaining trust and achieving best care for these patients.

6. **Titrating doses based on symptom.** Assessing dyspnea 'tolerability' turned out to be an imperfect metric for making titration decisions. Patients "tolerate" poor symptom control and have learned to do so over a long period of time. While some might rate a dyspnea intensity of 8/10 as tolerable others could state 5/10 as intolerable. This speaks to the subjective nature of dyspnea and its perception.

7. **Opioid preparations/dosing.** While most preferred the sustained-release pill, some patients could not tolerate a switch, preferring to remain on a lower dose of immediate-release morphine syrup. In addition, we had to accept that small changes in opioid doses, i.e. from 1 –1.5 mg QID, particularly in elderly and frail patients, were often sufficient to achieve an acceptable level of dyspnea or avoid side effects, dose changes that are not possible with current sustained-release preparations. Nevertheless most patients ultimately were pleased to move away from more frequent and less convenient dosing of a short-acting liquid. Ideally there would be a lower dose (5mg) sustained release product. This is not available currently.

8. **Assessments/measurements***:* From previous experience in studies of advanced COPD we anticipated a poor rate of completion of quantitative tools but found instead a remarkable willingness, both on the parts of patients and their caregivers to complete our questionnaires. We heard from many that they viewed this research as highly important and wished to share their experiences with others.

Conclusion

When carefully initiated and titrated, opioids are a helpful and acceptable intervention for refractory dyspnea in advanced COPD. Benefits outweigh risks and many patients experience sustained benefits over months. These findings should provide confidence in opioid prescribing in accordance with recent professional society recommendations and practice guidelines[11].

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Competing interests: None declared

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Opioid for Dyspnea ELIGIBILITY CHECKLIST Study/ Log ID Number: _ _ -- _ _ _
Pre/Post Opioid Clinical Trial (G. Rocker)…….. Site # Sequence #

Please complete this form each time you assess a patient identified as potentially eligible/ suitable *– (see Section C). For eligible patients who consent, assign a study number in sequence from the Eligible Patients Enrolled on Study log sheet. For ineligible patients or eligible patients who do not consent, assign a number in sequence from the Ineligible/ No Consent Patients log sheet (30 series).*

Section A – Inclusion Criteria Patient's Primary Diagnosis ***must*** be COPD:

☐ **1. Age > 55 and Chronic Obstructive Pulmonary Disease (COPD) – Severe or Moderate**

		Eligible
Severe – *one or more of*: ➢ severe SOB resulting in the patient being too breathless to leave the house ➢ breathlessness after dressing/ undressing (MRC 5) ➢ chronic respiratory failure ($PaCO_2$ > 45) ➢ clinical signs of right heart failure	(√) one or more: ☐ ☐ ☐ ☐	(√) ☐
OR		
Moderate – ➢ SOB such that patient has to stop walking after 100 metres or a few minutes on ground level (MRC 3-4) *AND -- one or more of:* ➢ acute exacerbation of COPD requiring hospital admission within the last year ➢ ICU admission ➢ forced expiratory volume in 1 sec ≤ 30% predicted ➢ BMI <21 *AND --* ➢ MRC 4 patients with baseline CRQ-D score >5	(√) ☐ *AND* one or more: ☐ ☐ ☐ ☐ *AND:* ☐	(√) ☐
➢ Primary reason for opioid prescription is for the treatment of dyspnea?	(√) ☐	(√) ☐

Section B – Exclusion Criteria

Circle *Yes* or *No* beside each of the criteria to determine if excluded. If eligible, continue completing checklist. If excluded, assign a 30-sequence ID number and skip to Section C if a family caregiver is available to approach.

		Eligible
➢ Acute exacerbation of COPD in the past month?	YES (excluded) *or* NO (eligible)	(√) ☐
➢ patient is not able to communicate in English or French	YES (excluded) *or* NO (eligible)	
➢ LOC is impaired due to medications, coma, encephalopathy, etc	YES (excluded) *or* NO (eligible)	
➢ Patient has overlap syndrome (i.e. COPD and sleep disordered breathing)	YES (excluded) *or* NO (eligible)	

Section C – Suitability Assessment

Check (√) to confirm study suitability has been confirmed.

			Eligible
Patient has been *assessed and deemed suitable* by: ❖ attending physician ❖ bedside nurse ❖ case manager ❖ other (specify): *and confirmed by research coordinator* to be a suitable candidate for the study	(√) one ☐ ☐ ☐ ☐	(√) ☐ ☐	(√) ☐
Cognitive abilities, physical stamina, psychological state indicate patient able to tolerate interview.			

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Section D – Informed Consent *If patient meets all above eligibility criteria*, request study consent.

		Eligible
Informed consent has been obtained --> Yes -- Date signed: _____ No (*explain*): _____	(√) ..... ☐	(√) ☐
Comments:		

Section E – Identifying Information Record below identifying information for eligible consenting patients.

Patient Initials: _____ (First) -- _____ (Middle) -- _____ (Last) Date of Birth: _____ (Year) -- _____ (Month) -- _____ (Day)

Name of Research Coordinator: _____

Signature: _____ Date (*Year/ Month/ Day*): _____

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Drowsiness/Sleepiness

This is unlikely to be an issue with our low dose approach. Nevertheless, it is advisable to avoid driving or operating heavy machinery for 24 hours after any increase in dose. If drowsiness does occur, it is likely to disappear after a day or two. Other sedative medications are likely to increase the drowsiness effects of morphine and should be avoided if possible.

Mental Clouding/Concentration Difficulties

Temporary feelings of 'foggy head" or difficulty focusing or concentrating may occur at higher doses or any time a dose is changed/increased. Again, this usually disappears after a day or two. Using any sedative medications and alcohol along with your morphine can make these symptoms worse. Once your body has adjusted to a given dose of morphine, it is unlikely that these symptoms will continue.

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Nausea

Some people will experience nausea and sometimes vomiting when starting on morphine or when the dose is increased. This is usually mild and resolves within a day or two. This is not likely to be a problem with the schedule of doses you will be taking. If nausea is troublesome, you will be provided with anti-nausea medication until your body adjusts.

What if I think I am experiencing side effects?

You will be asked regularly about side effects you may be having and how you are able to cope with them. If you are having troublesome side effects or have questions about what to do, **contact the study coordinator (name of local coordinator) at (phone number(s)).**

What if I want to stop morphine?

After the first two weeks, it is important that you do not stop your morphine abruptly. If you feel you are experiencing side effects or do not wish to continue taking morphine for other reasons**, contact the study coordinator or one of the study doctors. All of their contact information is on your "Research Team Contact Page" and your study consent form.**

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[Insert local health authority logo here]

Patient Guide to Starting Morphine for Shortness of Breath

During the first week of the study, you will start taking a very low dose of morphine. The dose will be increased after a few days and then gradually adjusted each week until we reach the dose that works best at relieving your shortness of breath and gives you minimal side effects. Your shortness of breath will be monitored every week over the next 6 weeks. Depending on your overall comfort, your dose will stay the same or be slowly adjusted up or down as necessary.

Starting slowly and at low dose will decrease the chances of side effects, but it may also take time to experience benefits in terms of your breathing. It is important to continue to take the medication regularly.

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Initial Dose Schedule Week One

Your morphine will come in a liquid form. The strength will be 1 mg for every 1 mL (1mg/1mL).

Days 1 and 2: Take 1 dose of morphine 0.5 mL at 8 am and 8 pm
Days 3 and 4: Take 1 dose of morphine 0.5 mL at 8am, 12noon, 4pm and 8pm
Days 5, 6 & 7: Take 1 dose of morphine **1 mL** at 8 am, 12noon, 4pm and 8pm

At the end of week one, you should be taking 1 mL of morphine liquid, 4 times per day.

You will be contacted at the end of each week to determine if your dose needs to be increased or left the same. At the end of week six, if you choose to remain on morphine, you may be switched to a slow release pill that only needs to be taken once or twice daily (this will depending on the type of medication chosen by your study doctor and whether or not this option would be right for you).

Common Side Effects

Most side effects from morphine occur at starting doses much higher than you will be taking. It is important to realize that most common side effects of morphine, if they do occur, are temporary and disappear after a few days. You are unlikely to note any side effects in the first week or two, but may be more likely to experience them as your dose slowly increases. You will be monitored regularly for side effects, and if you are experiencing side effects we will adjust your medication accordingly. If necessary we may reduce or stop it altogether. By increasing your dose very gradually, we are decreasing the chances that you will experience any troublesome effects.

Constipation

This is the most common side effect and the only one that tends to persist after your body has adjusted to the morphine. You will receive a regular stool softener/laxative to prevent constipation and the study doctor will decide which medication will be best for you. The dose of the softener/laxative will be adjusted to maintain regular bowel habit. It is important to pay close attention to changes in your stool so that you can deal with any signs of constipation as early as possible.

This is a sample guide to prevent significant constipation:

Start at level 0.
LEVEL 0: Senokot•S - 2 tablets at bedtime.
If no bowel movement within 48 hours then go to Level 1.
LEVEL 1: Senokot•S - 2 tablets 2 times a day.
If no bowel movement in 24 hours, then go to Level 2.
LEVEL 2: Senokot•S 3 tablets 2 times a day.
If no bowel movement in 24 hours, then go to Level 3.
LEVEL 3: Senokot•S 4 tablets 2 times a day or as directed by physician, pharmacist and/or nurse.

Remain on whatever level provides a comfortable bowel movement every 1-3 days

• If you have stools more frequently than your usual pattern, decrease dose of Senokot•S by half.
• If you experience loose stool, do not take Senokot•S for 1 day.
• If you have no bowel movement for 3 days **OR** more than 3 loose stools in 1 day, call the study coordinator.

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Appendix 2

Pt STATUS AND DEMOGRAPHICS Form

Study PID Number: __ __ -- __ __ __

Pre/Post Opioid Clinical Trial (G. Rocker)..... Site # Sequence#

Patient Initials: _____ -- _____ -- _____ (First / Middle / Last)
Date of Birth: _____ -- _____ -- _____ (Year / Month / Day)
Gender (circle one): F *or* M

Marital status of Patient:		(√) one
1	Married or living as married	
2	Widowed	
3	Never married	
4	Divorced or separated	
5	Other (specify):	

Oxygen therapy: No _____ Yes _____ Flowrate _____ Saturation _____% FEV1 _____

Ethnic/ Racial Group – *self assessed*		(√) one
1	Asian/ Pacific Islander	
2	African/ Black North American	
3	Caucasian	
4	East Indian	
5	Native Canadian	
6	Other (specify);	

Education *-- highest level achieved*		(√) one
1	Elementary school or less	
2	Some high school	
3	High school graduate	
4	Some college (including CEGEP)/ trade school	
5	College diploma (including DEC)/ trade school	
6	Attended university	
7	University degree	
8	Post graduate degree	
9	Other (specify):	

Employment Status					
			Has your employment status changed as a result of your illness? ❑ No *or* ❑ Yes – *complete below*:		
<u>Current</u> Employment Status		(√) one	If YES: What was your <u>previous</u> employment status?		(√) one
1	Employed full time		1	Employed full time	
2	Employed part time		2	Employed part time	
3	On paid leave		3	On paid leave	
4	On unpaid leave		4	On unpaid leave	
5	Self-employed		5	Self-employed	
6	Retired		6	Retired	
7	Not employed		7	Not employed	
8	Other (specify):		8	Other (specify):	

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Appendix 2

0	None	Comorbid Illnesses – *circle all number codes that apply*			
	Myocardial				Cancer/ Immune
1	Angina		Endocrine	25	Any tumour
2	Arrhythmia	15	Diabetes Type 1 or II	26	Lymphoma
3	Valvular disease	16	Diabetes with end organ damage	27	Leukemia
4	Myocardial infarction			28	AIDS
5	CHF or heart disease	17	Obesity and/ or BMI >30 (weight in kg/ ht in metres)^2	29	Metastatic solid tumour
	Vascular				Psychological
6	Hypertension		Renal	30	Anxiety or panic disorder
7	Peripheral vascular disease or claudication	18	Moderate or severe renal disease	31	Depression
8	Cerebrovascular disease		Gastrointestinal		Muskoskeletal
	Pulmonary	19	Mild liver disease	32	Arthritis (rheumatoid or osteo-)
9	COPD, emphysema			33	Denegerative disc disease (back, spinal stenosis, severe chronic back pain)
10	Asthma	20	Moderate/ severe liver disease	34	Osteoporosis
	Neurologic			35	Connective tissue disease
11	Dementia	21	GI bleeding		Miscellaneous
12	Hemiplegia (paraplegia)	22	Inflammatory bowel disease	36	Visual impairment (cataracts, glaucoma, macular degeneration)
13	Stroke or TIA	23	Peptic ulcer disease	37	Hearing impairment (very hard of hearing even with hearing aid)
14	Neurologic illnesses (e.g. MS or Parkinsons)	24	GI disease (hernia, reflux)		

Palliative Performance Scale (PPS) – *Please circle the applicable % level in the far left column*

%	Ambulation	Activity and Evidence of Disease	Self Care	Intake	Consciousness Level
100	Full	Normal Activity No Evidence of Disease	Full	Normal	Full
90	Full	Normal Activity Some Evidence of Disease	Full	Normal	Full
80	Full	Normal Activity with Effort Some Evidence of Disease	Full	Normal or Reduced	Full
70	Reduced	Unable Normal Job/Work Some Evidence of Disease	Full	Normal or Reduced	Full
60	Reduced	Unable Hobby/House Work Significant Disease	Occasional Assistance Necessary	Normal or Reduced	Full or Confusion
50	Mainly Sit/Lie	Unable to Do Any Work Extensive Disease	Considerable Assistance Required	Normal or Reduced	Full or Confusion
40	Mainly in Bed	As Above	Mainly Assistance	Normal or Reduced	Full or Drowsy or Confusion
30	Totally Bed Bound	As Above	Total Care	Reduced	Full or Drowsy or Confusion
20	As above	As Above	Total Care	Minimal Sips	Full or Drowsy or Confusion
10	As above	As Above	Total Care	Mouth Care Only	Drowsy or Coma
0	Death	-	-	-	-

Please continue on page 2 ---------->

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Appendix 2

Questions about living arrangements:

a) Tell us about the community in which you live?

❑ Mostly Rural ❑ Mostly Urban ❑ Mixed

b) Does your home have more than one level, i.e., flights of stairs?

❑ No ❑ Yes - if yes, how many? _____

c) Are you able to drive yourself to medical appointments?

❑ Yes ❑ No longer drive, rely on _____ ❑ No vehicle

d) Do you have children?

❑ No ❑ Yes - number of children _____

e) Would you say you are a follower of a particular religious tradition? e.g., Christianity, Judaism, Islam, etc.

❑ No ❑ Yes _____ If Christian, denomination _____

f) How important are these beliefs to you at this point in your life?

❑ Unimportant ❑ Somewhat unimportant ❑ neither important nor unimportant ❑ Somewhat important ❑ Important

g) Do you have an advance directive (living will or power of attorney for health care decisions)?

❑ No ❑ Don't know ❑ Yes: advance directive ___; power of attorney _____

h) If you were given the choice, where would you prefer to die (for example: at home, in hospital, elsewhere)?

❑ Don't know ❑ at home ❑ in hospital ❑ elsewhere (please specify) _____

For coordinator/interviewer:

Qualitative interview completed: No _____ Yes _____ date: _____

Completed scales/questionnaires:

VAS……..…… ☐ Global "helpfulness" questions……..…… ☐

QoL……..…….. ☐ HADS…….…..... ☐

CRQ……..…… ☐ NOSE……..…….. ☐

Sign and date this form

Name of Site Research Coordinator/Interviewer: _____

Signature: _____ Date Completed: _____ _____ _____

Year Month Day

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Appendix 3

PRELIMINARY INTERVIEW GUIDES
Pre/Post Opioid Clinical Trial (G. Rocker)

Pre Opioids

- Thinking back over the past few months, what has life like for you living with this illness?

    - How would you describe your quality of life—why, what changed over the course of your illness? What was most difficult for you about this? What was your breathing like? Were there things you could not do? Why/what stopped you?
    - What about relationships, e.g., with spouse, family members, friends—do you think your illness has affected any of these; how?
    - What about formal care—how satisfactory has it been for you? (doctors, nurses, respiratory therapists, clinic visits, hospitals, home support)
    - Other effects?
    - Greatest fears? (exacerbations; getting help; burden to loved ones)
    - Hopes?

- What bothers you most right now? What would you most like to change if you could?

    - Quality of life (factors mentioned in #1), breathing
    - Relationships (as above)
    - Formal care (as above)
    - Other things
    - Fears (as above)
    - Hopes

- What were your thoughts when your doctor first talked to you about starting morphine? (fears, concerns, hopes, understandings)

    - Did you talk about any of these things with your doctor, then or since?
    - How did your doctor explain it to you? (what did s/he say)
    - Have your thoughts changed since being on the morphine?

- Is there anything else you think might be helpful for other COPD patients, doctors, or families to know about this illness?

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Appendix 3

Post Opioids

- What was life like for you before you began taking the morphine?

- How would you describe your quality of life—why, what changed over the course of your illness? What was most difficult for you about this? What was your breathing like? Were there things you could not do? Why/what stopped you?

    - What about relationships, e.g., with spouse, family members, friends—do you think your illness has affected any of these; how?
    - What about formal care—how satisfactory has it been for you? (doctors, nurses, respiratory therapists, clinic visits, hospitals, home support)
    - Other effects?
    - Greatest fears? (exacerbations; getting help; burden to loved ones)
    - Hopes?

- Since you started the morphine has anything changed? What and how?

    - Quality of life (factors mentioned in #1), breathing
        - Relationships (as above)
        - Formal care (as above)
        - Other things
        - Fears (as above)
        - Hopes

- Have your thoughts about taking morphine changed since the time your doctor first talked to you about starting you on this drug? (fears, concerns, hopes, understandings)

- Did you talk about any of these things with your doctor, then or since?
    - What do you think has made the difference (if there is one)
    - Is there anything that might change your mind about these drugs (if no change has occurred and fears/concerns persist)?

- Is there anything else you think other COPD patients, families, doctors, or the research team should know about this morphine experience?

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Appendix 3

Summary

The interview guide is designed to elicit patients' stories about their experiences both pre and post opioid therapy. The semi-structured open-ended questions will be the basis of a conversation (45-60 minutes with the patient alone) concerning changes patients have noticed in their quality of life, dyspnea/other symptoms, significant relationships, satisfaction with and type of formal care (has being on morphine enabled conversations with formal caregivers that might not otherwise have taken place—or at least had not taken place prior to beginning the morphine intervention?), fears/concerns, and hope(s). Part of the focus of the analysis of this data will be on the balance of benefits:harms (positives, negatives, neutrals) as assessed by the patients themselves and the role this plays in how they rate the formal care they have experienced.

As well, it should provide some insight into how particular patients interpret this option and how that may or may not affect their experience with it (and/or their compliance), i.e., what beginning a morphine intervention signals to them, how they fit it into their understanding of the illness, its severity (worsening, ?dying), cultural, familial, and historical views of morphine (and/or narcotics use more generally, i.e., addiction risk, association with cancer pain, etc.).

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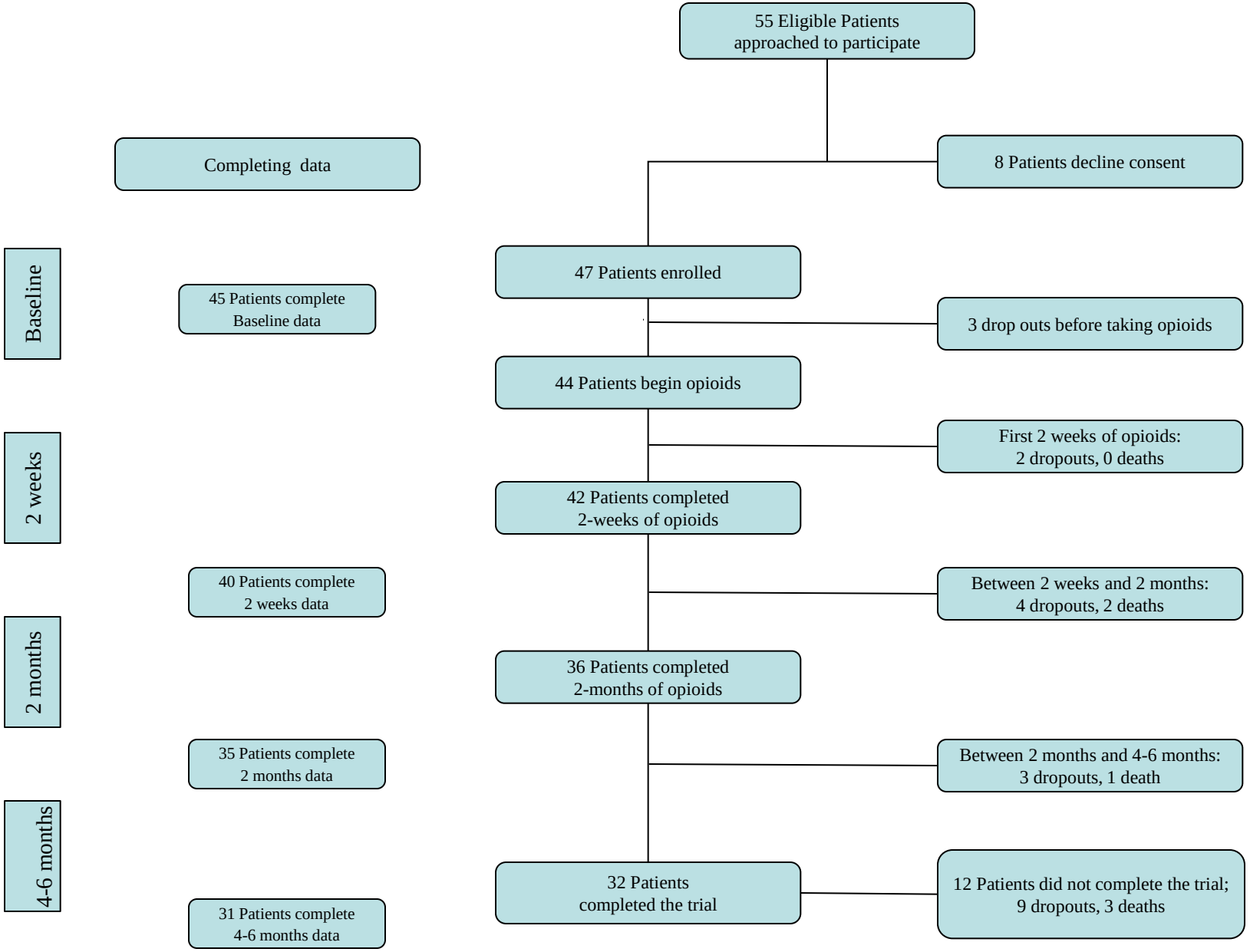

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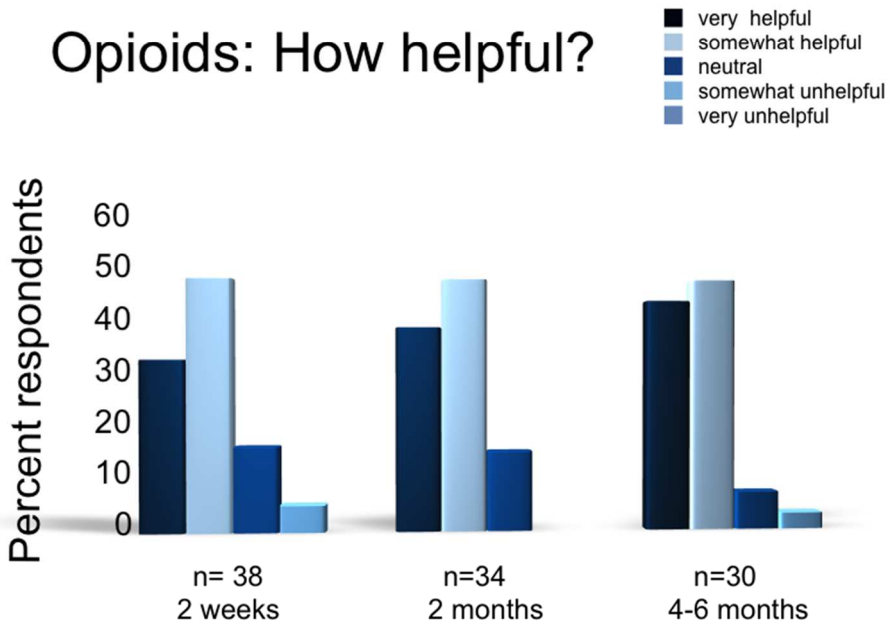

Figure 2: Global ratings of "helpfulness" of opioids on 5-point Likert scale
301x220mm (72 x 72 DPI)

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Figure 4b: Chronic Respiratory Questionnaire

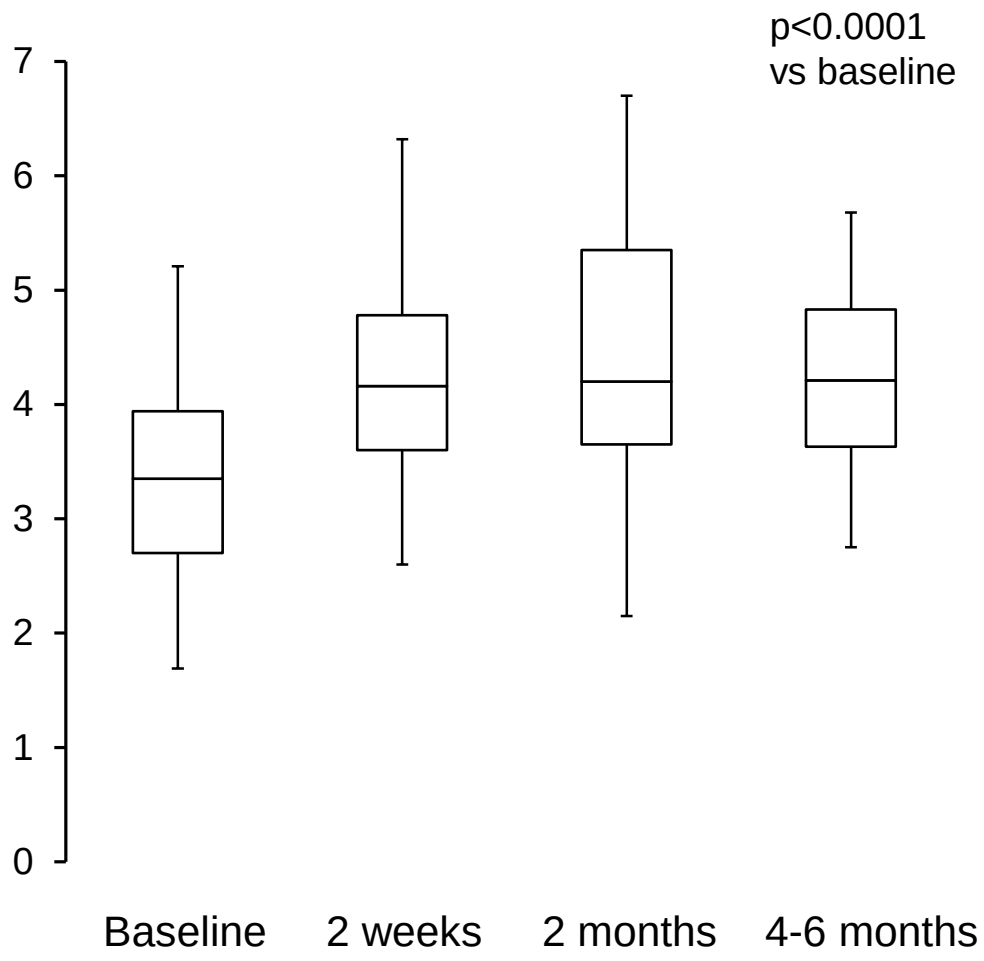

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Figure 4a: CRQ Dyspnea Domain

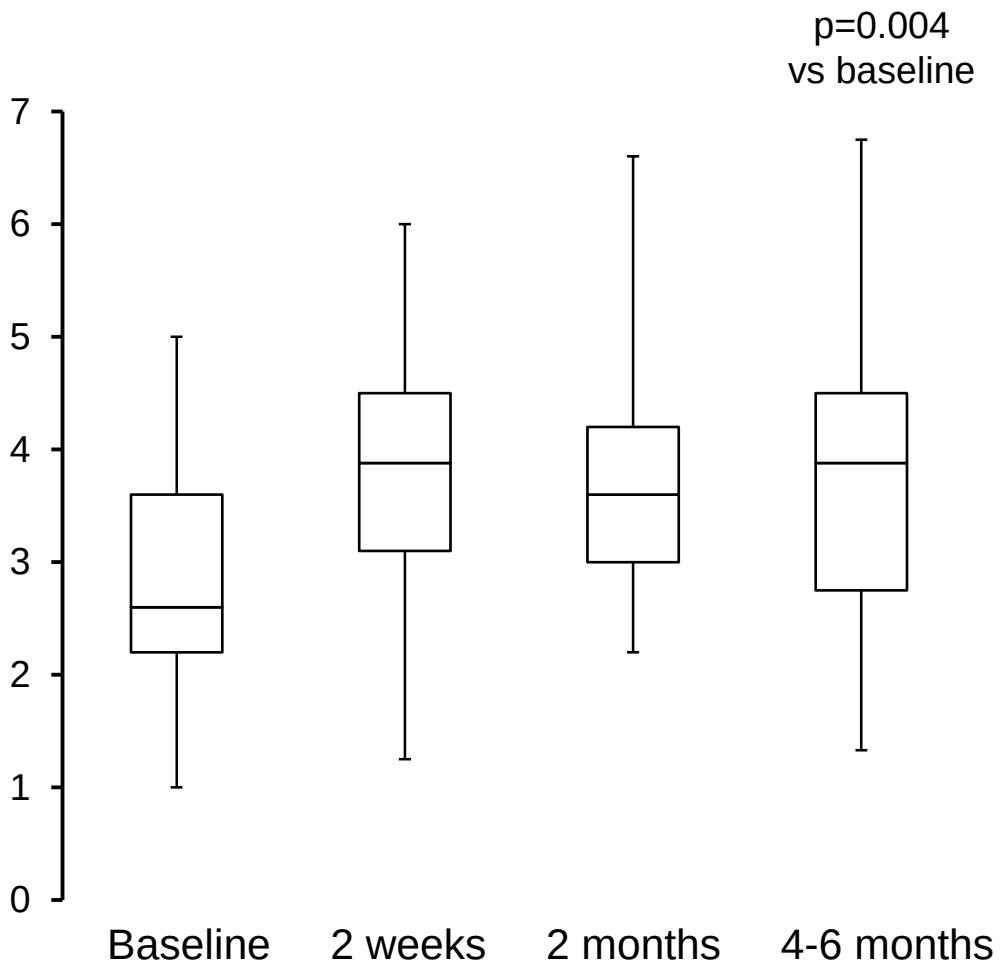

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Figure 3: Dyspnea Numerical Rating Scale

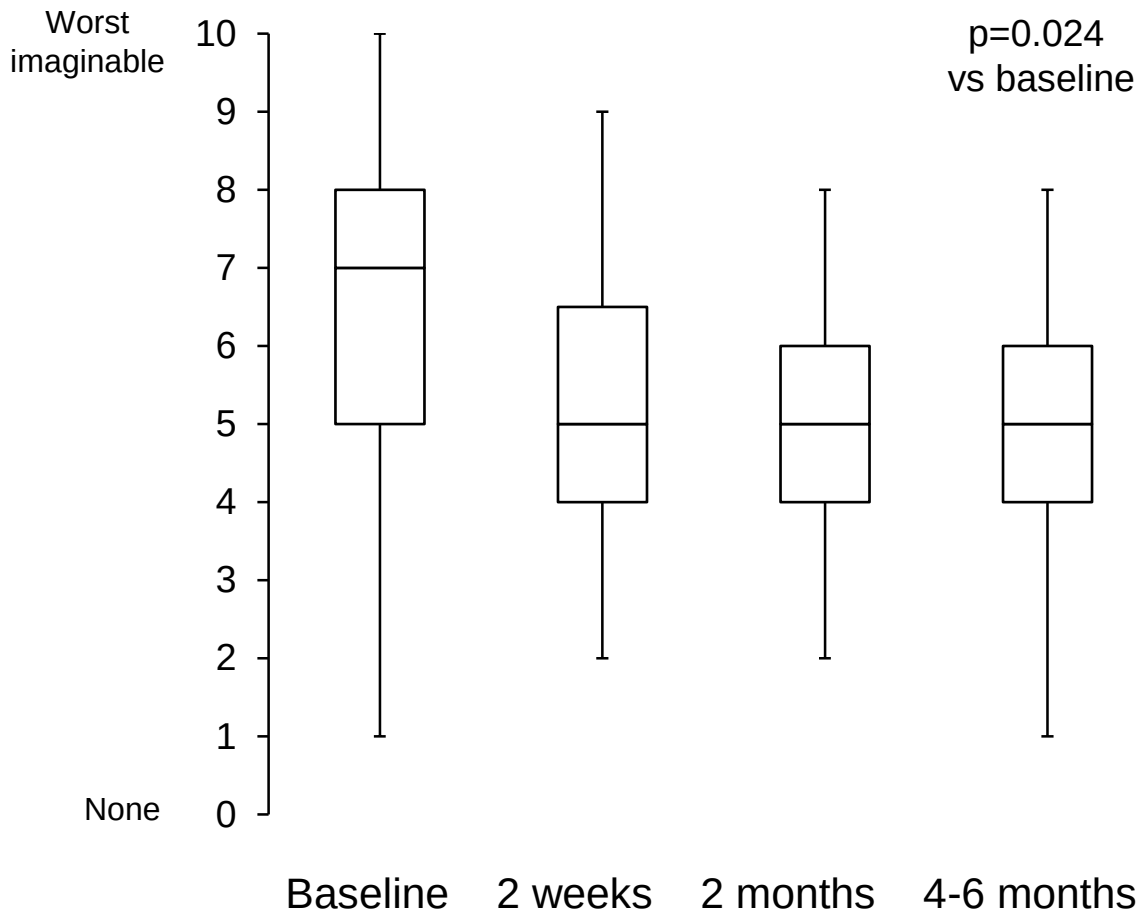

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Table 1. Opioid Dosing and Titration Schedule

Timetable	Drug and Dosage	Dyspnea Outcome Measure
Day 1, 2 Day 3, 4 Day 5, 6, 7	Morphine sulfate 0.5mg BID Morphine sulfate 0.5mg q4h Morphine sulfate 1.0mg q4h	At end of week 1 if score on Likert scale ≥ 4 (i.e. dyspnea somewhat intolerable or completely intolerable, (see appendix) then:
Week 2	Morphine sulfate 2.0 mg q4h	At end of week if dyspnea score >4 as above, then:
Week 3	Morphine sulfate 3.0mg q4h	At end of week if dyspnea score >4 as above, then:
Week 4	Morphine sulfate 5.0mg q4h	At end of week if dyspnea score >4 as above, then:
Week 5 +	Ongoing titration weekly with increase of 30-50% based on dyspnea severity and side effects. If patient develops persistent intolerable side effects, revert to previous tolerated dose and re-evaluate in 48 hours. If side effects persist, rotate to hydromorphone or taper dose by 50% per day and discontinue over 72 hours.	
Week 6+	Patients who remain on a stable dose of opioid i.e. have not required titration in the preceding 2 weeks can switch to a sustained release preparation	

Table 2. Timelines

Data Collection	Baseline	Titration	Opioid study period	
	week 0	week 2	2 months +/- 1 wk	4-6 months +/- 1 wk
Demographic information	x			
Qualitative interviews	x		x	x
Dyspnea: CRQ-D, NRS, tolerability	x	x	x	x
HRQoL: CRQ, : QOLLTI–P,	x x	x	x x	x x
HADS	x		x	x
Potential side effects (NOSE)	x	x	x	x
Overall opioid effect		x	x	x
Opioid responsiveness score	x		x	x

Abbreviations: CRQ-D, Chronic Respiratory Questionnaire Dyspnea domain; HRQoL, Health-Related Quality of Life; NRS, Numerical Rating Scale; HADS, Hospital Anxiety and Depression Scale; NOSE, Numerical Opioid Side Effects; ORS, Opioid Responsiveness Score.

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Table 3. Baseline Demographic Data

Characteristic		Patients, n (%)
Gender	Female	26 (58)
	Male	19 (42)
Age (years), median (range)		74 (51-89)
Location:		
Nova Scotia		31 (69)
New Brunswick		8 (18)
Saskatchewan		6 (13)
Dyspnea severity	MRC 5	37 (82)
	MRC 4	8 (18)
FEV_1 % predicted mean (SD) (where available)		26.8 (8.9) n=34
Long Term Oxygen Usage		27/45 (60)
Education High school graduate with no additional education (or less)		25 (58)

MRC, Medical Research Council Dyspnea Scale; FEV_1, Forced Expiratory Volume in 1 second.

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Table 4. Changes in Quantitative Measures for Patients from Baseline to 6 Months

	Baseline n=45	2 weeks n=39	2 months n=34	4-6 months n=31	Difference Baseline: 4-6 months (n=31)	P-value
HRQoL,						
CRQ	3.45 (2.8-4.0)	4.22 (3.8-4.7)	4.13 (3.6-4.8)	4.21 (3.6-4.8)	0.63 (0.14-1.31)	< 0.0001
QOLLTI-P	5.0 (3.0-6.0)		5.5(4.0-7.5)	5.0(5.0-7.0)	1 (0-2)	0.053
Dyspnea						
NRS	7.0 (5.0-8.0)	5.0 (4.0-7.0))	5.0 (4.0-6.0)	5.0 (4.0-6.))	-2.0 (-3.0-1.0)	0.024
CRQ-D	2.75 (2.3-3.6)	3.88 (3.0-4.5)	3.60 (3.0-4.2)	3.88 (2.8-4.5)	0.58 (0-1.35)	0.004
Anxiety/Depression		*				
HADS (A)	8.0 (6-10))		7.0 (3.0-9.0)	7.0 (4.0-11.0)	-1.5 (-3.0-1.0)	0.15
HADS (D)	8.0 (6-11)		6.0(4.0-8.0)	7.0 (5.0-9.0)	-1.0 (-3.0-0.0)	0.08

All measurements are reported as median (IQR).
* HADS was not measured at 2 weeks since we did not anticipate any changes in anxiety/depression at this early stage of opioid therapy.
Abbreviations: HRQoL, Health-Related Quality of Life; CRQ, Chronic Respiratory Questionnaire; CRQ-D, Chronic Respiratory Questionnaire Dyspnea domain; NRS, Numerical Rating Scale; HADS, Hospital Anxiety and Depression Scale; NOSE, Numerical Opioid Side Effects; ORS, Opioid Responsiveness Score.

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Table 5. Patient Self-reported Side Effects of Opioids[20]

Symptoms	Baseline n=45	2 weeks n=39	2 months n=34	4-6 months n=31
Nausea/Vomiting/ lack of appetite	2.23 (2.89)	1.29 (2.13)	1.62 (2.69)	1.71 (2.24)
Fatigue/ trouble concentrating/ hallucinations/drowsiness	3.15 (2.83)	2.10 (2.73)	2.38 (2.62)	2.97 (2.56)
Constipation	2.80 (2.80)	2.92 (3,38)	3.33 (3.21)	3.32 (3.11)
Itching	2.03 (2.90)	1.23 (1.84)	1.66 (2.27)	1.52 (2.61)
Decreased sexual desire	4.61 (4.79)	2.22 (3.80)	2.39 (4.15)	3.68 (4.61)
Dry Mouth	5.23 (3.53)	3.31 (2.78)	4.59 (3.17)	4.52* (3.08)
Abdominal Pain	2.80 (3.13)	1.36 (1.69)	1.88 (2.48)	1.77 (2,22)
Sweating	1.58 (2.05)	1.36 (1.91)	1.33 (1.83)	1.42 (1.95)
Headaches/dizziness	2.08 (2.41)	1.95 (2.45)	1.76 (2.50)	1.84 (2,37)
Urine retention	1.39 (2,14)	1.21 (2.09)	1.15 (1.86)	1.23 (1.61)
Minimum completion rate for any question	36/45 80%	36/39 92%	31/34 91%	28/31 90%

Self-reported side-effects range from 0=not present to 10=bad. Values are presented as mean (SD).
* $p<0.05$ versus baseline

Table 6a: Reasons to Continue (or not) with Opioids

	I would strongly prefer to continue on opioids because they provide significant relief from dyspnea	I would strongly prefer to continue on opioids because they provide significant improvement in my quality of life	I would prefer to continue on opioids because they provide significant relief from dyspnea	I would prefer to continue on opioids because they provide significant improvement in my quality of life	I do not have any feelings or preferences one way or another for continuing on opioids or not	I would prefer to be tapered off opioids	I would strongly prefer to be tapered off opioids
2 months n=34 responses	8 (24%)	13 (38%)	1 (3%)	8 (24%)	3 (8%)	0 (0%)	1 (3%)
4-6 months n=40 responses	12 (30%)	9 (22.5%)	7 (17.5%)	10 (25%)	2 (5%)	0 (0%)	0 (0%)

Table 6b: Balancing Benefits and Side Effects of Opioids

	Opioids continue to provide significant relief from dyspnea with minimal side effects	Opiods continue to provide significant relief from dyspnea but with significant side effects	Opioids continue to provide significant relief from dyspnea but with side effects that are not tolerable	Opioids are providing some relief from dyspnea and the side effects are tolerable	Opioids are providing some relief from dyspnea but the side effects are not tolerable	Opioids are not providing much relief from dyspnea but the side effects are tolerable	Opioids are not providing much relief from dyspnea but the side effects are not tolerable
2 months n=32 responses	16 (50%)	0 (0%)	0 (0%)	14 (44%)	0 (0%)	1 (3%)	1 (3%)
4-6 months n=29 responses	13 (45%)	2 (7%)	0 (0%)	10 (34%)	0 (0%)	4 (14%)	13

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