Ann Hutchinson, BA Hons
Miriam J. Johnson, MD, FRCP, MRCP, MBChB(hons)
Hull York Medical School, University of Hull
York, United Kingdom
E-mail: hyah6@hyms.ac.uk

David Currow, B Med, MPH, PhD, FRACP, FAChPM
Hull York Medical School, University of Hull
York, United Kingdom
University of Technology Sydney
Sydney, NSW, Australia

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References

1. Abernethy AP, Wheeler JL. Total dyspnoea. Curr Opin Support Palliat Care 2008;2:110–113.

2. Ahmadi Z, Sandberg J, Shannon-Honson A, Vandersman Z, Currow DC, Ekström M. Is chronic breathlessness less recognised and treated compared with chronic pain? A case-based randomised controlled trial. Eur Respir J 2018;52:1800887.

3. Johnson MJ, Bowden JA, Abernethy AP, Currow DC. To what causes do people attribute their chronic breathlessness? A population survey. J Palliat Med 2012;15:744–750.

4. Currow DC, Dal Grande E, Ferreira D, Johnson MJ, McCaffrey N, Ekström M. Chronic breathlessness associated with poorer physical and mental health-related quality of life (SF-12) across all adult age groups. Thorax 2017;72:1151–1153.

5. Hutchinson A, Pickering A, Williams P, Bland JM, Johnson MJ. Breathlessness and presentation to the emergency department: a survey and clinical record review. BMC Pulm Med 2017;17:53.

6. Nunez S, Hexdall A, Aguirre-Jaime A. Unscheduled returns to the emergency department: an outcome of medical errors? Qual Saf Health Care 2006;15:102–108.

7. Johnson M, Yorke J, Hansen-Flaschen J. Towards an expert consensus to delineate a clinical syndrome of chronic breathlessness. Eur Respir J 2017;49.

8. Mularski RA, Reinke LF, Carrieri-Kohlman V, et al. An official American Thoracic Society workshop report: assessment and palliative management of dyspnea crisis. Ann Am Thorac Soc 2013;10:S98–S106.

9. Simon ST, Higginson IJ, Benalia H, et al. Episodes of breathlessness: Types and patterns—a qualitative study exploring experiences of patients with advanced diseases. Palliat Med 2013;27:524–532.

10. Ekström M, Bajwah S, Bland JM, Currow DC, Hussain J, Johnson MJ. One evidence base; three stories: do opioids relieve chronic breathlessness? Thorax 2018;73:88–90.

11. Bausewein C, Schunk M, Schumacher P, Dittmer J, Bolzani A, Booth S. Breathlessness services as a new model of support for patients with respiratory disease. Chronic Respir Dis 2018;15:48–59.

12. Hopkinson NS, Baxter N. Breathing SPACE—a practical approach to the breathless patient. NPJ Prim Care Respir Med 2017;27:5.

13. Spathis A, Booth S, Moffat C, et al. The Breathing, Thinking, Functioning clinical model: a proposal to facilitate evidence-based breathlessness management in chronic respiratory disease. NPJ Prim Care Respir Med 2017;27:27.

14. Hutchinson A, Barclay-Klingle N, Galvin K, Johnson MJ. Living with breathlessness: a systematic literature review and qualitative synthesis. Eur Respir J 2018;51:1701477.

Challenges in Recruiting Patients to a Controlled Feasibility Study of a Drug for Opioid-Induced Constipation: Lessons From the Population With Advanced Cancer

To the Editor:

Clinical research is difficult in populations with advanced illness because patients have a high disease burden and short life expectancy, poor functional status and high distress, or an unpredictable course characterized by changing therapies and an increased risk of adverse events. This is reflected in the paucity of published trials; fewer than 1% are conducted in an advanced illness population. The lack of randomized trials means that high-quality evidence plays a small role in defining best clinical practices and standards for end-of-life care.[1]

We initiated a small multicenter trial of oral naloxegol (Movantik®) in patients with advanced cancer, cancer-related pain, and opioid-induced constipation (OIC) to determine the feasibility of a larger definitive study. Large controlled studies in populations with chronic noncancer pain recruited adequately and confirmed naloxegol's efficacy.[2,3] Two previous studies in patients with cancer-related pain were closed prematurely owing to poor patient enrollment.[4] Our study attempted to address the recruitment issues identified in previous efforts, but recruitment challenges again led to early study closure. This experience may provide insight into the problem of poor trial enrollment in populations with advanced illness.

Methods

A multicenter randomized, placebo-controlled study was designed to assess the feasibility of a definitive trial of naloxegol for OIC in a population with advanced cancer. Secondary outcomes included tolerability, safety, and efficacy.

Study Design and Sample Size

To reduce patient burden, the design included fewer study visits and a shorter double-blind

intervention than prior studies. The maximum study duration was 35 days, and the main elements were as follows: 1) a prescreening during which patients were determined to be potentially eligible for the study; 2) consent process; 3) seven-day baseline assessment/OIC confirmation period to confirm eligibility; 4) randomization followed by 14-day period of double-blind treatment with naloxegol 25 mg daily or identical placebo; and 5) a 14-day period of treatment with open-label naloxegol 25 mg daily for those who completed the double-blind period. Three sites in the U.S. participated: Four Seasons Compassion for Life in Western North Carolina; MJHS Institute for Innovation in Palliative Care in New York; and Hospice of the Western Reserve in Cleveland, Ohio. Planned study enrollment was one to two patients per site per month, and it was estimated that 64 patients would be screened to obtain 44 randomly assigned patients over 15 months.

Eligibility

Inclusion and exclusion criteria were as follows: 1) age ≥18 years; 2) able to follow instructions in English, give informed consent, and respond to questionnaires; 3) active cancer with a life expectancy of eight weeks or more and a Palliative Performance Status scale ≥30%; 4) if receiving chemotherapy, completion of ≥1 cycle of the current regimen; 5) pain due to the neoplasm or its treatment for two weeks or more; 6) daily treatment with ≥20 mg morphine or its equivalent for at least one week; 7) daily laxative use at a stable dose for seven days or more and a willingness to continue this for seven days; and 8) OIC defined according to Rome IV criteria.[5] Patients were excluded for any clinically significant brain pathology; intra-abdominal neoplasm or other gastrointestinal disorders; opioid-refractory pain; elevated liver enzymes; pregnancy or lactation; myocardial infarction within six months or symptomatic congestive heart failure or peripheral vascular disease; active substance or alcohol abuse; use of prohibited medications or any investigational medication within the previous 30 days.

Recruitment

Patients were recruited from outpatient oncology offices, palliative care clinics, and hospice and palliative care sites (home, facilities, or inpatient hospice unit). Initial prescreening, conducted at each site, involved review of information in the medical record or from a treating clinician. When prescreening suggested eligibility, the patient was contacted by clinical staff to determine interest. The research coordinator contacted an interested patient to provide information about the study. At the request of the patient, family members were often consulted, and additional information was sometimes obtained from treating clinicians. If the patient was eligible and expressed interest, a visit was scheduled to obtain written informed consent before any study-specific procedures were initiated. Consenting patients whose eligibility was confirmed entered the seven-day baseline period.

Analysis

The primary reason for study exclusion of prescreened and screened patients was recorded, as were tolerability and safety data.

Results

The study was closed after 24 months owing to poor enrollment. A total of 590 patients were prescreened and initially appeared to fulfill eligibility criteria, but 578 were subsequently excluded or declined to consent (Table 1). Most of those excluded ($N = 414$, 71.6%) were medically ineligible based on additional information from the patient/family or from a treating clinician (Table 1). Of the patients who remained medically eligible after the patient was contacted (140, 24.2%), the majority declined to consent to the study. The most common reasons included family reluctance because the patient was too ill and a lack of interest in clinical research.

Of the 12 patients who were eligible and consented, seven did not fulfill eligibility for randomization during the seven-day baseline/OIC confirmation period. Two subjects failed to meet the constipation criteria, two had rapid decline, one had an abnormal laboratory result, one had a history of abdominal neoplasm,

Table 1

Reason for Exclusion of Prescreened Patients During a Controlled Feasibility Trial of Naloxegol for Opioid-Induced Constipation in Advanced Cancer Patients

Total, *N*	578
Medically ineligible, *n* (%)	414 (71.6%)
Low PPS or prognosis	228 (39.5)
Not constipated	43 (7.4)
Abdominal/colon/gastric cancer	34 (5.9)
Cognitive decline/dementia/stroke	32 (5.5)
Brain cancer/brain metastases	27 (4.7)
Prohibited/unstable medications	18 (3.1)
Not taking opioids	14 (2.4)
GI disease	9 (1.6)
No active cancer	4 (0.7)
Safety concerns	2 (0.3)
Substance abuse	2 (0.3)
Pain not cancer related	1 (0.2)
Patient or family declined, *n* (%)	140 (24.2)
Other, *n* (%)	24 (4.2)
Non−English speaking	17 (3)
Moved to facility	4 (0.7)
Unknown, *n* (%)	2 (0.3)
Cannot reach, *n* (%)	1 (0.2)

PPS = Palliative Performance Score; GI = gastrointestinal.

and one was noncompliant. Of the five randomized patients, one withdrew consent. Four patients completed the study and no adverse events reported were related to the study drug.

Comment

This trial was designed to determine the feasibility of a multicenter, placebo-controlled randomized trial of naloxegol for the treatment of OIC in patients with advanced cancer. Compared to earlier studies, patients with relatively poor performance status and short prognosis were eligible to enroll, study duration was shorter, and the number of visits was reduced.[3,6] Unexpectedly, the major challenge as the study unfolded was patient recruitment. Although many potentially eligible patients were identified across the three study sites using a brief prescreening, 98% of patients did not proceed with the study. Most patients were determined to be ineligible because of disease severity, and many of those who were eligible declined because a family member perceived the patient as too ill.

Although our experience suggests that recruitment may be better if eligibility is expanded to include patients with less severe illness, this may be difficult in studies of cancer symptoms because symptoms are more prevalent in advanced cancer and studies compete with cancer treatment trials until relatively late in the illness. Although the literature on study recruitment is limited,[7] our experience is consistent with previous research in populations with advanced illnesses. It underscores the need to project higher screening numbers and lower rates of enrollment when planning similar trials in populations with advanced cancer.

Our experience cannot be assumed to apply to studies that use hospitals or oncology practices as the primary sites of recruitment or studies that are designed to evaluate other types of treatments or cancer subpopulations. Moreover, our data do not clarify the number of recruitment barriers per patient. Nonetheless, our experience highlights the potential for recruitment challenges that must be addressed in conducting high-quality supportive care clinical trials in populations with advanced illness. Future efforts will be needed to develop study procedures that address these challenges and improve the research capability in this field.

Janet Bull, MD, MBA
Lindsay Bonsignore, PhD
Lisa Massie, CCRC
Four Seasons Compassion for Life
Flat Rock, North Carolina
USA

Alexa Riggs, MPH
MJHS Institute for Innovation in Palliative Care
New York, New York
USA

Helena Knotkova, PhD
MJHS Institute for Innovation in Palliative Care
New York, New York
USA
Department of Family and Social Medicine
Albert Einstein College of Medicine
Bronx, New York
USA

Charles Wellman, MD
Hospice of the Western Reserve
Cleveland, Ohio
USA

Russell Portenoy, MD
MJHS Institute for Innovation in Palliative Care
New York, New York
USA
Department of Family and Social Medicine
Albert Einstein College of Medicine
Bronx, New York
USA
Department of Neurology
Albert Einstein College of Medicine
Bronx, New York
USA
MJHS Hospice and Palliative Care
New York, New York
USA

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References

1. Tieman J, Sladek R, Currow D. Changes in the quantity and level of evidence of palliative and hospice care literature: the last century. J Clin Oncol 2008;26:5679–5683.

2. Leonard J, Baker DE. Naloxegol: treatment for opioid-induced constipation in chronic non-cancer pain. Ann Pharmacother 2015;49:360–365.

3. Chey WD, Webster L, Sostek M, Lappalainen J, Barker PN, Tack J. Naloxegol for opioid-induced constipation in patients with noncancer pain. N Engl J Med 2014;370:2387–2396.

4. von Roenn JH, Tack J, Barker PN, Lowe ES, Fleischmann C, Sostek M. Challenges in patient recruitment during KODIAC-06, a randomized, placebo-controlled, double-blind, multicenter, phase 3 trial of naloxegol in patients with neoplasia and opioid-induced constipation (OIC), in Multinational Association of Supportive Care in Cancer 2013;S1–S301. Poster presented

at: MASCC/ISOO International Symposium on Supportive Care in Cancer; June 2013; Berlin, Germany.

5. Schmulson MJ, Drossman DA. What is New in Rome IV. J Neurogastroenterol Motil 2017;23:151–163.

6. Webster L, Chey WD, Tack J, Lappalainen J, Diva U, Sostek M. Randomised clinical trial: the long-term safety and tolerability of naloxegol in patients with pain and opioid-induced constipation. Aliment Pharmacol Ther 2014;40:771–779.

7. Dunleavy L, Walshe C, Oriani A, Preston N. Using the 'Social Marketing Mix Framework' to explore recruitment barriers and facilitators in palliative care randomised controlled trials? A narrative synthesis review. Palliat Med 2018;32:990–1009.