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A protocol for a discrete choice experiment: understanding patient preferences for managing chronic non-cancer pain

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Abstract

Introduction

High rates of chronic non-cancer pain (CNCP), concerns about adverse effects including dependence among those prescribed potent pain medications, the recent evidence supporting active rather than passive management strategies and a lack of funding for holistic programs have resulted in challenges around decision making for treatment among clinicians and their patients. Discrete choice experiments (DCE) are one way of assessing and valuing treatment preferences. Here, we outline a protocol for a study that assesses patient preferences for CNCP treatment.

Methods and analysis

A literature review, a focus group, and individual interviews informed the development of treatment characteristics and levels to be used in the DCE. Two groups of participants will contribute to the DCE: participants from a longitudinal cohort of patients receiving opioids for CNCP and a convenience sample of patients recruited through a consumer pain advocacy organisation (Pain Australia) and their social media and website.

Ethics and dissemination

Ethics approval was obtained from the UNSW Sydney Human Ethics committee HC16511 (for the focus group discussions, the one-on-one interviews, and online survey) and HC16916 (for the cohort). A lay summary will be made available on the NDARC website, Pain Australia's website. Peer review papers will be submitted, and it is expected the results will be presented at relevant pain management conferences nationally and internationally. These results will also be used to improve understanding of treatment goals between clinicians and those with CNCP.

Strengths and Limitations of this study

- This DCE will elucidate how people with CNCP value different treatments that include both medicines and holistic goals of pain management.
- Our DCE will be conducted in two samples: an already recruited diverse cohort of people with CNCP who have been prescribed opioids and a novel group of people with CNCP who may not have been prescribed opioids, recruited via social media.
- The samples will include the most common pain conditions such as chronic back and neck problems, arthritis and migraines.

- The study will estimate marginal willingness to pay for changes in number of medications, level of pain interference, risk of addiction and preference of service provider.
- The preference discrete choice experiment surveys will be undertaken in Australia, which could affect generalisability to other settings.

Introduction

These are challenging times for both people with chronic non-cancer pain (CNCP) and those to whom they turn for treatment. Despite a significant increase in opioids being prescribed for CNCP in countries such as the United States, Canada and Australia[1-3] there is insufficient evidence on the long term effectiveness of use[4].

Accompanying the increase in opioid prescribing there has been a concurrent increase in harms, with more than 64,000 opioid overdoses in the US[5], 1,300 in Australia[6] in 2016 and 8,440 in Europe[7]. Responses to minimise harms associated with pharmaceutical opioids include increased regulatory controls such as prescription monitoring programs and limiting access to over-the-counter codeine in Canada, Australia, and the United States[8]. Other strategies have focused on improved clinical practice, including limiting maximum doses and prescriber education[9]. However, taken together with busy general practitioners, a shortage of pain and addiction specialists, fear of addiction and the lack of accessible and affordable alternatives for pain management this has led to increased anxiety amongst many with CNCP[10]

With chronic pain reported by approximately one-third of the US population[11] and thirty-nine percent of a representative Australian sample[12], and potential rates of dependence varying between 1% and 24% [13] among those who are prescribed potent analgesic medications, this represents a sizable challenge.

The benefits and harms of opioids for CNCP are complex and contextual, and include factors such as age, co-morbidities, health status, type and duration of pain, concurrent medications, patients' ability and willingness to self-manage. Under-treated CNCP adversely affects patients' wellbeing[10], but there are few data to inform the range of treatment choices available, maximise treatment outcomes and patient adherence, and minimise unintended consequences. In addition, prescribing decisions and patients' expectations are complicated by the common side effects from many medications used in CNCP, the lack of long-term evidence on efficacy[14-17], the development of tolerance, fears of dependence and lack of funding for non-drug based treatment options.

Recent evidence suggests that active rather than passive management strategies may 'retrain the brain' to reduce pain[18], and that a multidisciplinary approach is likely to produce the most optimal outcomes, but the cost and availability of alternative treatments may affect patients' treatment choices. Additionally, cognitive behaviour therapy has been found to help patients modify situational

factors and multi-modal therapies that combine exercise and related therapies with psychologically based approaches also help reduce pain and improve function more effectively than single modalities[19-21].

Preferences of clinicians and patients can impact prescribing patterns, uptake of interventions and treatment adherence, thus affecting the effectiveness of pain management[22]. It is important to understand why some people with CNCP resort to treatments that are expensive or without evidence of efficacy; and alternatively, why some stay on opioids long-term when not experiencing clinical benefit. For example, 34% of a cohort of CNCP participants reported that there had been no clinically significant change in their activity limitations, symptoms, emotions, and overall quality of life since starting opioids[23]. Significant proportions of the cohort were using complementary or alternative interventions for their pain which have limited or no evidence of efficacy in chronic pain[23, 24]. Additionally, they often report that attending physiotherapy, specialised exercise classes or psychotherapy was often prohibitively expensive and unfunded whereas medications and GP visits are at least partially covered by the Australian Medicare and Pharmaceutical Benefits Schemes.

The discrete choice methodology (DCE) allows for the identification of the preferences for various treatment options and potential trade-offs that individuals are willing to make. Moreover, DCEs have been widely used in the heath literature to elicit preferences from patient groups on health and non-health outcomes[25, 26]. Studies that have utilised the DCE methodology to examine patient preferences for managing CNCP have focused specifically on toleration of the adverse effects of nonselective NSAIDs and selective COX-2 inhibitors[27], management of neuropathic pain [28], surgical or non-surgical approaches for low back pain[29]; and acupuncture or infra-red treatments for low back pain[30]. These studies have often been limited to specific treatments[27-30] and to limited conditions[29, 30]. Here we outline a study protocol to elicit patient preferences for broader approaches to treatment for CNCP through use of a DCE by extending the range of attributes to encompass a wider range of treatment alternatives including holistic goals of pain management.

Aims

The aims of this study are to identify and value the factors that influence important treatment decisions among people living with CNCP, so we can better understand the choices they make. Specifically, we will assess:

1. preferences for medication

2. impact on choice of potential side effects including the possibility of addiction;
3. willingness to pay out of pocket for preferred options, and the extent to which costs may be a barrier;
4. the extent to which having input into treatment is important; and
5. the degree to which pain interference is tolerated.

Methods and analysis

Overview of the DCE

DCEs are a method of eliciting and quantifying preferences and exploring trade-offs between the attributes (characteristics) of a treatment (or a good or service). Attribute-based DCEs permit the exploration of preferences for treatment options while varying the levels of each attribute[26, 31, 32]. DCEs are based on Lancaster's economic theory of value (1966, 1971) and presume that individuals derive utility (or well-being) not from the good itself but rather from the attributes of that good[33, 34]. They rely on an individual's knowledge or perceptions of their own preferences, and on their ability to make trade-offs between alternatives in the presence of constraints such as money, time, availability and so on.

A DCE provides respondents with several hypothetical but reasonable choice sets. Each choice set consists of at least two alternatives which comprise a set of attributes each with various levels. Respondents are then asked to choose their preferred alternative in each choice set[33]. In making a choice, the respondent identifies the alternative that yields the highest utility to them. The attributes and their levels are important, as they drive decision making. When respondents make a choice, they make trade-offs between the levels of the various attributes which can then be analysed with logistic regressions. When a cost attribute is included, it is possible to indirectly estimate willingness-to-pay (WTP) values for particular attributes of treatment [35-38]. The dependent variable in the logistic regression represents the probability of choosing one alternative with specific attributes and levels over another. The independent variables are the attributes and their levels. It is feasible to account for heterogeneity through the use of covariates in a mixed logit (MXL) or latent class (LC) models [39, 40].

Theory

Consumer theory assumes deterministic behaviour, but choice theory asserts that individual behaviour is intrinsically probabilistic (random). Individuals have a concept of the value (indirect utility) for each choice, but the researcher does not know all the factors that might affect that choice. The utility

estimate consists of the knowable part and the random or unknowable parts. The random part may be due to unobserved attributes, unobserved preference variation, specification or measurement error, or inter-individual differences in utility as a result of variation in tastes[33, 41]. The utility function in the context of the DCE can be presented as follows:

$$U_{ij} = V_{ij} + \epsilon_{ij}, j = 1.....J \quad (1)$$

Where individual i will choose alternative j if, and only if, that alternative maximises their utility amongst all *J* alternatives. The utility (U) for individual *i* is conditional on choice *j* and decomposed into explainable or systematic V_{ij} and non-explainable or random component $\varepsilon_{ij.}$ V_{ij} can be further broken down into X_{jk}, a vector of attributes of the treatment, and Z, a vector of N characteristics of the individual i, and β and γ are the respective coefficients to be estimated for K attributes, with γ_n coefficients indicating the impact that the personal characteristics have on choice[42].

$$V_{ij} = \sum_{k=1}^{K} \beta_k X_{jk} + \sum_{n=1}^{N} \gamma_n Z_{in} \quad (2)$$

where y_{ij} is equal to 1 if alternative j is chosen, and 0 otherwise and 1 is the choice if and only if

$V_{ij} + \varepsilon_{ij} > V_{im} + \varepsilon_{im}$ for all $j \neq m$ which rearranges to

$V_{ij} - V_{im} > \varepsilon_{im} - \varepsilon_{ij.}$

Utilities are not observed, but by documenting the choices made, utilities can be estimated[43]. Additionally $(\varepsilon_{im} - \varepsilon_{ij})$ is not observed directly and so it is only possible to make observations up to a probability of occurrence with some distribution or density function. It is the choice of this distribution that affects interpretation of the probabilities [33]. Different density functions for the unobserved part of the utility ε_{ij} lead to different families of probabilistic discrete choice models.

Undertaking a DCE requires several steps including the selection of the relevant attributes and their levels, obtaining a feasible design for the DCE survey, constructing and administering the survey and determining the best-fitting model.

Patient and Public Involvement

The final survey tool (the DCE), including the framing of the question, was developed after a focus group discussion and multiple one-on-one discussions with persons who self-report as having CNCP. They were recruited from members of PainAustralia, a national peak body and pain advocacy organisation. As further described below, the important constructs from this qualitative work informed the choice of

attributes, levels and the final question. A lay summary of the findings will be made available on the NDARC website and PainAustralia's website.

Determining the attributes and levels for the DCE

The selection of attributes and their levels is a key step. There is a need to balance the number of attributes to adequately describe the good or service of interest; specifying too many attributes may hinder the respondents' decision making. The number of attributes will vary with the complexity of the good being considered, but typically studies include four to eight attributes. Undertaking qualitative work to inform the selecting and framing improves the relevance and applicability of the findings[44, 45].

Focus groups and telephone interviews with people living with CNCP

As a first step in this study, a literature review was undertaken to identify the important constructs to explore in subsequent focus groups and one-on-one discussions. The intent was to recruit 20 to 25 participants to participate in focus groups, however it became apparent this was going to be difficult due to health status of participants and location. Therefore, one focus group (N=3 participants) and 13 one-on-one telephone interviews were conducted with people who had CNCP, to elicit views on topics such as: self-management, knowledge of pain mechanisms, brain plasticity, relative importance of exercise, medications, choice of treatment provider, and barriers and facilitators to effective good treatment.

Telephone interviews with clinicians

Additionally, interviews were conducted with a range of clinicians including pain specialists, general practitioners (urban and rural), clinical nurse specialists, physiotherapists and addiction specialists (N=8). Clinician interviews elicited additional information on barriers and facilitators to treatment and views on current modalities of treatment for CNCP.

Determining the list of attributes and levels

Two authors (MSh and GC) reviewed the recorded interviews and catalogued characteristics (and identified potential levels). A list of attributes (and their levels) was generated and refined in discussions with other study collaborators. Attributes (and number of levels) selected were: number of medications (4), risk of addiction (4), side effects (2), pain interference (4), activity goals, source of information on pain (4), provider of pain care (4) and out of pocket costs (4).

Please insert Table 1 about here

Pilot Study

The DCE design

Having selected the attributes, levels, and number of alternatives (2), an experimental design for the survey was generated. Given the number of attributes and levels, a full factorial design including all possible combinations of attributes and their levels was not feasible. Therefore, a D-efficient experimental design that maximised model statistical efficiency by minimising the parameter standard errors was generated using Ngene[46]. The statistical efficiency of the design is improved if some prior information about these parameters is available. This can be coefficients from previous analysis or expert opinion[43, 46]. In the design for the pilot study, the prior coefficients were set to zero.

Pilot-testing attributes and levels

A pilot study was conducted among 33 people living with CNCP and who had been prescribed opioids. These data were used to refine the final list of attributes and levels. Specifically, the number of levels for the attribute 'risk of addiction to pain medications' was decreased from 4 to 2 levels (the two extremes), as respondents did not appear to distinguish between the middle two levels. (See Table 1 for final list of attributes and levels). The pilot testing was also used assess the ease with which participants could complete the experiment: 64% reported that it was easy/very easy to complete the scenario questions, 27% found it difficult and 9% found it very difficult.

Proposed study

Significant coefficients from the pilot study data (n=33) were used in the final experimental design. An efficient design of 80 scenarios, with 10 blocks was generated for the final design (each participant will be presented with one block of eight scenarios). See Table 2 for an example of a scenario.

Please insert Table 2 about here

Participants and survey procedures

There is no agreement on the correct sample size required for a DCE[47]. However, research has shown that in all DCE studies with efficient designs, model estimate precision increases rapidly at sample sizes greater than 150 and then flattens out at around 300[48]. It is also estimated that a minimum sample size of 200 respondents per sub-group be used for studies involving an analysis of differences between samples[49]. The proposed DCE will be administered to two groups of participants (see below) with the sample size of each group being 200 participants or greater.

Each participant will be randomly allocated to one of ten blocks with each block having eight DCE questions. In addition to the DCE questions, a range of demographic and covariates will be collected (i.e. age, gender, education, marital status) clinical characteristics (duration of pain, number and type of medications, pain interference scores).

(i) Pain and Opioids IN Treatment (POINT) prospective cohort study

The first source includes participants in POINT study, a national prospective cohort of 1,514 people living with CNCP [23]. The POINT study, currently in its fifth year, recruited participants through community pharmacies across Australia. Participants when recruited were: 18 years or older; living with CNCP (defined as pain lasting longer than three months); taking prescribed Schedule 8 opioids (including morphine, oxycodone, buprenorphine, methadone and hydromorphone) for CNCP for greater than six weeks when recruited; competent in English; mentally and physically able to participate in telephone and self-complete interviews; and did not have any serious cognitive impairments, as determined by the interviewer at the time of screening. The POINT cohort participants are interviewed annually over the phone, and the DCE survey will be included as part of the fifth-year interview. Participants in the POINT cohort study will be invited to participate in the survey and reasons for not participating will be recorded; the first consecutive 33 interviews of the fifth-year interview were administered the pilot study questionnaire and these participants will not complete a second DCE. The DCE will be mailed to participants prior to the date of interview along with an explanation of the study aims and consent forms. The DCE questionnaire will then be completed by the POINT interviewers over the phone as part of the regular POINT interview schedule. Covariates for the DCE will be drawn from baseline line data and the most recent interview.

(ii) Online survey of people living with CNCP

A second group of respondents will be recruited on-line through Pain Australia, a national peak body and pain advocacy organisation and through social media. This group will be asked to complete an identical DCE survey on-line (via Qualtrics, hosted at UNSW Sydney), plus selected demographic, pain characteristics, type of medications questions drawn from the POINT survey. Similar to the POINT cohort, participants who are eligible for the online survey will be aged 18 years or older, reside in Australia, and are living with CNCP (defined as pain lasting longer than three months). Unlike the POINT cohort, however, the online sample will not be required to have been prescribed Schedule 8 opioids (although this is not an exclusion in the online survey).

Links to the online survey will be posted on the Pain Australia website, the National Drug and Alcohol Research Centre website, and their associated Facebook pages, and twitter feeds. Recruitment will continue for four months (or until the current round of interviews of the cohort are complete) with the objective of achieving at least 200 surveys completed online. Respondents will be randomly allocated one of the ten blocks, and demographic and covariates will match collected from the POINT cohort.

Data analysis

The data from the two participant groups will be initially analysed separately, as their demographic and clinical characteristics may differ substantially (in terms of age, duration of pain, and current treatment modality). The analysis of the DCE responses will be analysed using Nlogit software[46]. Initially a multinomial logit model will be used. Mixed logit (MXL) and latent class (LC) analysis will be used to explore heterogeneity of responses. Number of medications, and out-of-pocket costs will be treated as continuous variables; all categorical variables will be effects coded which means the constant will not be confounded with the grand mean and coefficients for base levels can be estimated[50].

Article Summary

Strengths and Limitations of this study

The DCE approach offers great potential for informing clinicians as to patient preferences for pain management. Where preferences do not align with current evidence, the findings will provide an opportunity to develop strategies for improving knowledge. If preferred options are those that are known to be effective but also more expensive for the patient, the results can be used to inform policy makers. However, there are methodological limitations that are common to all DCEs. In our study, one challenge was to select attributes and levels that both reflect treatment for CNCP and outcomes but result in a practical number to include. Our choice to use eight attributes likely places higher cognitive demand on respondents but we sought to mitigate this by only requiring each person to complete eight DCE choices.

Our DCE will be conducted in a large, diverse sample of people living with CNCP, including the most common pain conditions such as chronic back and neck problems. This DCE differs from previous studies in that it will elucidate how people value different CNCP treatments, not just medications or not just surgery. This study will also permit the estimation of the marginal willingness to pay for different treatment options and outcomes.

Ethics and dissemination

Ethics approval was obtained from the UNSW Sydney Human Ethics committee HC16511 (for the focus group discussions, the one-on-one interviews, and online survey) and HC16916 (for the POINT cohort). A lay summary of the findings will be made available on the NDARC website and Pain Australia's website. Peer review papers will be submitted, and it is expected the results will be presented at relevant pain management conferences nationally and internationally. These results will also be used to improve understanding between clinicians and those with CNCP of goals of treatment.

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We thank members of PainAustralia for their support of this project through promoting it on their website and other social media, and for inviting members to participate in focus groups and other discussions. We also thank those who have completed the DCE survey and clinicians who contributed to the discussion of barriers and facilitators for managing chronic pain.

Author Contributions

MSh, BL, SN and MC are investigators on the grant (NHMRC, APP 1100822). MSh and GC reviewed recorded interviews, BL co-facilitated the focus groups, all authors participated in discussions to refine DCE attributes and levels. All authors provided extensive feedback on drafts of protocol.

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Competing interest statement

MSh and MS – nil

BL and SN report investigator-driven untied educational grants from Reckitt Benckiser/Indivior for studies of buprenorphine-naloxone and buprenorphine depot, the development of an opioid-related behaviour scale, and a study of opioid substitution therapy uptake among chronic non-cancer pain patients. BL has also received investigator-initiated untied educational grants for post-marketing surveillance studies of opioids from Mundipharma (a tamper-resistant oxycodone formulation) and Seqirus (tapentadol). These funders had no role in the design, conduct, or interpretation of these studies. These studies were unrelated to the current DCE protocol or broader POINT study. SN has

provided training around treatment of codeine dependence for which her institution received funding from Indivior.

GC reports investigator-driven untied educational grants from Reckitt Benckiser for the development of an opioid-related behaviour scale.

MC reports receiving fees from Mundipharma Limited for preparation and presentation of educational material.

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Table 1: Final attributes and levels

Attributes	Levels
Number of different medications taken on most days for pain	0, 2, 4 ,6
Known side effects of medications for pain	Mild, Moderate/Severe
Pain interference with daily activities	Never; Sometimes; Most of the time; Always
Pain care is managed by	GP only; Pain specialist; Multi-disciplinary pain management team; Myself
Risk of addiction to pain medication	Risk of 3 in 100 people or 25 in 100 people who are taking strong pain medications*
Activity goals of treatment	Able to undertake activities of daily living; Do exercises at home, including walking, most days; Participate in regular exercise classes (gym /hydrotherapy classes); Practice mindfulness regularly
Source of information on pain and pain management	None; From a doctor; By reading/ Online; From a pain management course
Out of pocket costs per month (i.e. for medications, doctor, physio or psychologist visits, or other activities you would need to pay for to help you manage your pain)	$50, 100, 200 or 300 per month

** Initial choice of four levels decreased to two after pilot study, see below*

Table2: Example of scenario

	Treatment A	Treatment B
Pain medications per day	2	4
Known side effects of medications	Mild	Moderate / severe
Pain interference	Never	Never
Pain care is managed by	Myself	GP only
Risk of addiction to pain medications	3 out of in 100 people	25 in 100 people
Activity goals of treatment	Do exercises at home, including walking	Do exercises at home, including walking
Source of information on pain	From my doctor	By reading/ online
Out of pocket costs per month	300	300
My choice is (please choose A or B)	☐	☐

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A protocol for a discrete choice experiment: understanding patient medicine preferences for managing chronic non-cancer pain

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A protocol for a discrete choice experiment: understanding patient medicine preferences for managing chronic non-cancer pain

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Abstract

Introduction

High rates of chronic non-cancer pain (CNCP), concerns about adverse effects including dependence among those prescribed potent pain medications, the recent evidence supporting active rather than passive management strategies and a lack of funding for holistic programs have resulted in challenges around decision making for treatment among clinicians and their patients. Discrete choice experiments (DCE) are one way of assessing and valuing treatment preferences. Here, we outline a protocol for a study that assesses patient preferences for CNCP treatment.

Methods and analysis

A final list of attributes (and their levels) for the DCE experiment were generated using a detailed iterative process. This included a literature review, a focus group, and individual interviews with those with CNCP and clinicians who treat people with CNCP. From this process a list of attributes was obtained. Following a review by study investigators including pain and addiction specialists, pharmacists and epidemiologists, the final list of attributes were selected (number of medications, risk of addiction, side effects, pain interference, activity goals, source of information on pain, provider of pain care and out of pocket costs). Specialised software was used to construct an experimental design for the survey. The survey will be administered to two groups of participants, those from a longitudinal cohort of patients receiving opioids for CNCP and a convenience sample of patients recruited through Australia's leading pain advocacy body (Pain Australia) and their social media and website. The data from the two participant groups will be initially analysed separately, as their demographic and clinical characteristics may differ substantially (in terms of age, duration of pain, and current treatment modality). Mixed logit (MXL) and latent class (LC) analysis will be used to explore heterogeneity of responses.

Ethics and dissemination

Ethics approval was obtained from the UNSW Sydney Human Ethics committee HC16511 (for the focus group discussions, the one-on-one interviews, and online survey) and HC16916 (for the cohort). A lay summary will be made available on the NDARC website, Pain Australia's website. Peer review papers will be submitted, and it is expected the results will be presented at relevant pain management conferences nationally and internationally. These results will also be used to improve understanding of treatment goals between clinicians and those with CNCP.

Strengths and Limitations of this study

- This DCE will elucidate how people with CNCP value different treatments that include both medicines and holistic goals of pain management.
- Our DCE will be conducted in two samples: an already recruited diverse cohort of people with CNCP who have been prescribed opioids and a novel group of people with CNCP who may not have been prescribed opioids, recruited via social media.
- The samples will include the most common pain conditions such as chronic back and neck problems, arthritis and migraines.
- The study will estimate marginal willingness to pay for changes in number of medications, level of pain interference, risk of addiction and preference of service provider.
- The preference discrete choice experiment surveys will be undertaken in Australia, which could affect generalisability to other settings.

Introduction

These are challenging times for both people with chronic non-cancer pain (CNCP) and those to whom they turn for treatment. Despite a significant increase in opioids being prescribed for CNCP in countries such as the United States, Canada and Australia[1-3] there is insufficient evidence on the long term effectiveness of use[4].

Accompanying the increase in opioid prescribing there has been a concurrent increase in harms, with more than 64,000 opioid overdoses in the US[5], 1,300 in Australia[6] in 2016 and 8,440 in Europe[7]. Responses to minimise harms associated with pharmaceutical opioids include increased regulatory controls such as prescription monitoring programs and limiting access to over-the-counter codeine in Canada, Australia, and the United States[8]. Other strategies have focused on improved clinical practice, including limiting maximum doses and prescriber education[9]. However, taken together with busy general practitioners, a shortage of pain and addiction specialists, fear of addiction and the lack of accessible and affordable alternatives for pain management this has led to increased anxiety amongst many with CNCP[10]

With chronic pain reported by approximately one-third of the US population[11] and thirty-nine percent of a representative Australian sample[12], and potential rates of dependence varying between 1% and 24% [13] among those who are prescribed potent analgesic medications, this represents a sizable challenge.

The benefits and harms of opioids for CNCP are complex and contextual, and include factors such as age, co-morbidities, health status, type and duration of pain, concurrent medications, patients' ability and willingness to self-manage. Under-treated CNCP adversely affects patients' wellbeing[10], but there are few data to inform the range of treatment choices available, maximise treatment outcomes and patient adherence, and minimise unintended consequences. In addition, prescribing decisions and patients' expectations are complicated by the common side effects from many medications used in CNCP, the lack of long-term evidence on efficacy[14-17], the development of tolerance, fears of dependence and lack of funding for non-drug based treatment options.

Recent evidence suggests that active rather than passive management strategies may 'retrain the brain' to reduce pain[18], and that a multidisciplinary approach is likely to produce the most optimal outcomes, but the cost and availability of alternative treatments may affect patients' treatment choices. Additionally, cognitive behaviour therapy has been found to help patients modify situational factors and multi-modal therapies that combine exercise and related therapies with psychologically

based approaches also help reduce pain and improve function more effectively than single modalities[19-21].

Preferences of clinicians and patients can impact prescribing patterns, uptake of interventions and treatment adherence, thus affecting the effectiveness of pain management[22]. It is important to understand why some people with CNCP resort to treatments that are expensive or without evidence of efficacy; and alternatively, why some stay on opioids long-term when not experiencing clinical benefit. For example, 34% of a cohort of CNCP participants reported that there had been no clinically significant change in their activity limitations, symptoms, emotions, and overall quality of life since starting opioids[23]. Significant proportions of the cohort were using complementary or alternative interventions for their pain which have limited or no evidence of efficacy in chronic pain[23, 24]. Additionally, they often report that attending physiotherapy, specialised exercise classes or psychotherapy was often prohibitively expensive and unfunded whereas medications and GP visits are at least partially covered by the Australian Medicare and Pharmaceutical Benefits Schemes.

The discrete choice methodology (DCE) allows for the identification of the preferences for various treatment options and potential trade-offs that individuals are willing to make. Moreover, DCEs have been widely used in the heath literature to elicit preferences from patient groups on health and non-health outcomes[25, 26]. Studies that have utilised the DCE methodology to examine patient preferences for managing CNCP have focused specifically on toleration of the adverse effects of nonselective NSAIDs and selective COX-2 inhibitors[27], management of neuropathic pain [28], surgical or non-surgical approaches for low back pain[29]; and acupuncture or infra-red treatments for low back pain[30]. These studies have often been limited to specific treatments[27-30] and to limited conditions[29, 30]. Here we outline a study protocol to elicit patient preferences for broader approaches to treatment for CNCP through use of a DCE by extending the range of attributes to encompass a wider range of treatment alternatives including holistic goals of pain management.

Aims

The aims of this study are to identify and value the factors that influence important treatment decisions among people living with CNCP, so we can better understand the choices they make. Specifically, we will assess:

1. preferences for medication
2. impact on choice of potential side effects including the possibility of addiction;
3. willingness to pay out of pocket for preferred options, and the extent to which costs may be a barrier;

4. the extent to which having input into treatment is important; and
5. the degree to which pain interference is tolerated.

Methods and analysis

Overview of the DCE

DCEs are a method of eliciting and quantifying preferences and exploring trade-offs between the attributes (characteristics) of a treatment (or a good or service). Attribute-based DCEs permit the exploration of preferences for treatment options while varying the levels of each attribute[26, 31, 32]. DCEs are based on Lancaster's economic theory of value (1966, 1971) and presume that individuals derive utility (or well-being) not from the good itself but rather from the attributes of that good[33, 34]. They rely on an individual's knowledge or perceptions of their own preferences, and on their ability to make trade-offs between alternatives in the presence of constraints such as money, time, availability and so on.

A DCE provides respondents with several hypothetical but reasonable choice sets. Each choice set consists of at least two alternatives which comprise a set of attributes each with various levels. Respondents are then asked to choose their preferred alternative in each choice set[33]. In making a choice, the respondent identifies the alternative that yields the highest utility to them. The attributes and their levels are important, as they drive decision making. When respondents make a choice, they make trade-offs between the levels of the various attributes which can then be analysed with logistic regressions. When a cost attribute is included, it is possible to indirectly estimate willingness-to-pay (WTP) values for particular attributes of treatment [35-38]. The dependent variable in the logistic regression represents the probability of choosing one alternative with specific attributes and levels over another. The independent variables are the attributes and their levels. It is feasible to account for heterogeneity through the use of covariates in a mixed logit (MXL) or latent class (LC) models [39, 40].

Theory

Consumer theory assumes deterministic behaviour, but choice theory asserts that individual behaviour is intrinsically probabilistic (random). Individuals have a concept of the value (indirect utility) for each choice, but the researcher does not know all the factors that might affect that choice. The utility estimate consists of the knowable part and the random or unknowable parts. The random part may be due to unobserved attributes, unobserved preference variation, specification or

measurement error, or inter-individual differences in utility as a result of variation in tastes[33, 41]. The utility function in the context of the DCE can be presented as follows:

$$U_{ij} = V_{ij} + \epsilon_{ij}, j = 1.....J \quad (1)$$

Where individual i will choose alternative j if, and only if, that alternative maximises their utility amongst all *J* alternatives. The utility (U) for individual *i* is conditional on choice *j* and decomposed into explainable or systematic V_{ij} and non-explainable or random component $\varepsilon_{ij.}$ V_{ij} can be further broken down into X_{jk}, a vector of attributes of the treatment, and Z, a vector of N characteristics of the individual i, and β and γ are the respective coefficients to be estimated for K attributes, with γ_n coefficients indicating the impact that the personal characteristics have on choice[42].

$$V_{ij} = \sum_{k=1}^{K} \beta_k X_{jk} + \sum_{n=1}^{N} \gamma_n Z_{in} \quad (2)$$

where γ_{ij} is equal to 1 if alternative j is chosen, and 0 otherwise and 1 is the choice if and only if

$V_{ij} + \varepsilon_{ij} > V_{im} + \varepsilon_{im}$ for all $j \neq m$ which rearranges to

$V_{ij} - V_{im} > \varepsilon_{im} - \varepsilon_{ij.}$

Utilities are not observed, but by documenting the choices made, utilities can be estimated[43]. Additionally ($\varepsilon_{im} - \varepsilon_{ij}$) is not observed directly and so it is only possible to make observations up to a probability of occurrence with some distribution or density function. It is the choice of this distribution that affects interpretation of the probabilities [33]. Different density functions for the unobserved part of the utility ε_{ij} lead to different families of probabilistic discrete choice models.

Undertaking a DCE requires several steps including the selection of the relevant attributes and their levels, obtaining a feasible design for the DCE survey, constructing and administering the survey and determining the best-fitting model.

Patient and Public Involvement

The final survey tool (the DCE), including the framing of the question, was developed after a focus group discussion and multiple one-on-one discussions with persons who self-report as having CNCP. They were recruited from members of PainAustralia. Pain Australia is Australia's leading pain advocacy body representing the interests of a membership that includes health, medical, research and consumer organisations it works to improve the quality of life of people living with pain and to facilitate implementation of the National Pain Strategy Australia-wide. As further described below, the important constructs from this qualitative work informed the choice of attributes, levels and the

final question. A lay summary of the findings will be made available on the NDARC website and PainAustralia's website.

Determining the attributes and levels for the DCE

The selection of attributes and their levels is a key step. There is a need to balance the number of attributes to adequately describe the good or service of interest; specifying too many attributes may hinder the respondents' decision making. The number of attributes will vary with the complexity of the good being considered, but typically studies include four to eight attributes. Undertaking qualitative work to inform the selecting and framing improves the relevance and applicability of the findings[44, 45].

Focus groups and telephone interviews with people living with CNCP

As a first step in this study, a literature review was undertaken to identify the important constructs to explore in subsequent focus groups and one-on-one discussions. The intent was to recruit 20 to 25 participants to participate in focus groups, however it became apparent this was going to be difficult due to health status of participants and location. Therefore, one focus group (N=3 participants) and 13 one-on-one telephone interviews were conducted with people who had CNCP, to elicit views on topics such as: self-management, knowledge of pain mechanisms, brain plasticity, relative importance of exercise, medications, choice of treatment provider, and barriers and facilitators to effective good treatment.

Telephone interviews with clinicians

Additionally, interviews were conducted with a range of clinicians including pain specialists, general practitioners (urban and rural), clinical nurse specialists, physiotherapists and addiction specialists (N=8). Clinician interviews elicited additional information on barriers and facilitators to treatment and views on current modalities of treatment for CNCP.

Determining the list of attributes and levels

The final list of attributes included in the DCE experiment were generated using a detailed iterative process. The first phase involved a literature review undertaken by MSh to inform the development of list of possible factors previously identified as influencing patient choice of pain treatments. This list was reviewed and further developed among the broader POINT study investigators who include pain and addiction specialists, pharmacists and epidemiologists.

These attributes developed in the first phase of the study became the basis of (a) focus group discussions with patients and (b) telephone interviews with clinicians. Two authors (MSh and GC) reviewed the recorded transcripts separately and independently analysed data thematically.

Attributes generated at this second phase included the following themes: potential side effects; concurrent medications; necessity to work / care for others; barriers; complementary medicine; multi-modal therapies; costs; time to onset of effect; adherence/compliance; risk of addiction; co-morbidities; and self-management.

In the final phase, this broader list was reviewed by the broader POINT study investigator team, and a final list of attributes (and their levels) was agreed. Attributes (and number of levels) selected were number of medications (4), risk of addiction (4), side effects (2), pain interference (4), activity goals, source of information on pain (4), provider of pain care (4) and out of pocket costs (4).

Please insert Table 1 about here

Pilot Study

The DCE design

Having selected the attributes, levels, and number of alternatives (2), an experimental design for the survey was generated. Given the number of attributes and levels, a full factorial design including all possible combinations of attributes and their levels was not feasible. Therefore, a D-efficient experimental design that maximised model statistical efficiency by minimising the parameter standard errors was generated using Ngene[46]. The statistical efficiency of the design is improved if some prior information about these parameters is available. This can be coefficients from previous analysis or expert opinion[43, 46]. In the design for the pilot study, the prior coefficients were set to zero.

Pilot-testing attributes and levels

A pilot study was conducted among 33 people living with CNCP and who had been prescribed opioids. These data were used to refine the final list of attributes and levels. Specifically, the number of levels for the attribute 'risk of addiction to pain medications' was decreased from 4 to 2 levels (the two extremes), as respondents did not appear to distinguish between the middle two levels. (See Table 1 for final list of attributes and levels). The pilot testing was also used assess the ease with which participants could complete the experiment: 64% reported that it was easy/very easy to complete the scenario questions, 27% found it difficult and 9% found it very difficult.

Proposed study

Significant coefficients from the pilot study data (n=33) were used in the final experimental design. An efficient design of 80 scenarios, with 10 blocks was generated for the final design (each participant will be presented with one block of eight scenarios). See Table 2 for an example of a scenario.

Please insert Table 2 about here

Participants and survey procedures

There is no agreement on the correct sample size required for a DCE[47]. However, research has shown that in all DCE studies with efficient designs, model estimate precision increases rapidly at sample sizes greater than 150 and then flattens out at around 300[48]. It is also estimated that a minimum sample size of 200 respondents per sub-group be used for studies involving an analysis of differences between samples[49]. The proposed DCE will be administered to two groups of participants (see below) with the sample size of each group being 200 participants or greater. To examine the possibility of different treatment preferences in people living with CNCP we included two distinct groups. The POINT cohort consist of participants who have been prescribed opioids for CNCP and have been on long-term opioids for an average of seven years at the time of the current study. The other sample includes CNCP recruited online. These participants are not necessarily prescribed opioids and we will examine the differences in treatment preferences between people prescribed and not prescribed opioids for CNCP.

Each participant will be randomly allocated to one of ten blocks with each block having eight DCE questions. In addition to the DCE questions, a range of demographic and covariates will be collected (i.e. age, gender, education, marital status) clinical characteristics (duration of pain, number and type of medications, pain interference scores).

(i) Pain and Opioids IN Treatment (POINT) prospective cohort study

The first source includes participants in POINT study, a national prospective cohort of 1,514 people living with CNCP [23]. The POINT study, currently in its fifth year, recruited participants through community pharmacies across Australia. Participants when recruited were: 18 years or older; living with CNCP (defined as pain lasting longer than three months); taking prescribed Schedule 8 opioids (including morphine, oxycodone, buprenorphine, methadone and hydromorphone) for CNCP for greater than six weeks when recruited; competent in English; mentally and physically able to participate in telephone and self-complete interviews; and did not have any serious cognitive impairments, as determined by the interviewer at the time of screening. The POINT cohort

participants are interviewed annually over the phone, and the DCE survey will be included as part of the fifth-year interview. Participants in the POINT cohort study will be invited to participate in the survey and reasons for not participating will be recorded; the first consecutive 33 interviews of the fifth-year interview were administered the pilot study questionnaire and these participants will not complete a second DCE. The DCE will be mailed to participants prior to the date of interview along with an explanation of the study aims and consent forms. The DCE questionnaire will then be completed by the POINT interviewers over the phone as part of the regular POINT interview schedule. Covariates for the DCE will be drawn from baseline line data and the most recent interview.

(ii) Online survey of people living with CNCP

A second group of respondents will be recruited on-line through Pain Australia, a national peak body and pain advocacy organisation and through social media. This group will be asked to complete an identical DCE survey on-line (via Qualtrics, hosted at UNSW Sydney), plus selected demographic, pain characteristics, type of medications questions drawn from the POINT survey. Similar to the POINT cohort, participants who are eligible for the online survey will be aged 18 years or older, reside in Australia, and are living with CNCP (defined as pain lasting longer than three months). Unlike the POINT cohort, however, the online sample will not be required to have been prescribed Schedule 8 opioids (although this is not an exclusion in the online survey).

Links to the online survey will be posted on the Pain Australia website, the National Drug and Alcohol Research Centre website, and their associated Facebook pages, and twitter feeds. Recruitment will continue for four months (or until the current round of interviews of the cohort are complete) with the objective of achieving at least 200 surveys completed online. Respondents will be randomly allocated one of the ten blocks, and demographic and covariates will match collected from the POINT cohort.

Data analysis

The data from the two participant groups will be initially analysed separately, as their demographic and clinical characteristics may differ substantially (in terms of age, duration of pain, and current treatment modality). The analysis of the DCE responses will be analysed using Nlogit software[46]. Initially a multinomial logit model will be used. Mixed logit (MXL) and latent class (LC) analysis will be used to explore heterogeneity of responses. Number of medications, and out-of-pocket costs will be treated as continuous variables; all categorical variables will be effects coded which means the

constant will not be confounded with the grand mean and coefficients for base levels can be estimated[50].

Tables of coefficients for the levels and covariates will be presented with relevant statistical measures including pseudo r-squared, log likelihood test, and the AIC to test for goodness of fit of the model. In addition, the marginal rate of substitution (the negative ratio between any two estimated coefficients) will be calculated. This will allow policy makers and clinicians to understand the relative importance of different attributes, and the respondents' willingness to give up some amount of one attribute in order to obtain more of another.

Article Summary

Strengths and Limitations of this study

The DCE approach offers great potential for informing clinicians as to patient preferences for pain management. Where preferences do not align with current evidence, the findings will provide an opportunity to develop strategies for improving knowledge. If preferred options are those that are known to be effective but also more expensive for the patient, the results can be used to inform policy makers. However, there are methodological limitations that are common to all DCEs. In our study, one challenge was to select attributes and levels that both reflect treatment for CNCP and outcomes but result in a practical number to include. Our choice to use eight attributes likely places higher cognitive demand on respondents but we sought to mitigate this by only requiring each person to complete eight DCE choices.

Our DCE will be conducted in a large, diverse sample of people living with CNCP, including the most common pain conditions such as chronic back and neck problems. This DCE differs from previous studies in that it will elucidate how people value different CNCP treatments, not just medications or not just surgery. This study will also permit the estimation of the marginal willingness to pay for different treatment options and outcomes. Although the marginal willingness to pay for preferred attributes will assist policy makers generally, some of the results may not be generalizable to resource-poor settings or countries without universal healthcare systems.

Ethics and dissemination

Ethics approval was obtained from the UNSW Sydney Human Ethics committee HC16511 (for the focus group discussions, the one-on-one interviews, and online survey) and HC16916 (for the POINT cohort). A lay summary of the findings will be made available on the NDARC website and Pain Australia's website. Peer review papers will be submitted, and it is expected the results will be presented at

relevant pain management conferences nationally and internationally. These results will also be used to improve understanding between clinicians and those with CNCP of goals of treatment.

Consent

Written consent was obtained from those who attended the focus groups and verbal consent was obtained from those who volunteered for phone interviews (researchers were only aware of first name of telephone participants). Consistent with UNSW ethics, for the on-line DCE survey, consent was implicit in the decision to complete the survey after reading the participation information sheet. For the POINT cohort, consent has previously been obtained from participants and the DCE is part of the scheduled interview.

Acknowledgement

We thank members of PainAustralia for their support of this project through promoting it on their website and other social media, and for inviting members to participate in focus groups and other discussions. We also thank those who have completed the DCE survey and clinicians who contributed to the discussion of barriers and facilitators for managing chronic pain.

Author Contributions

MSh was lead author and responsible for the study design, conducted the qualitative interviews and analysis, and the writing of the paper. GC and BL were involved qualitative interviews and its analysis. MSch contributed to the survey development and administration of the survey. MSh, BL, SN, MC and GC were involved in defining and selecting the attributes and levels. All authors provided detailed input to the paper.

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Competing interest statement

MSh and MS – nil

BL and SN report investigator-driven untied educational grants from Reckitt Benckiser/Indivior for studies of buprenorphine-naloxone and buprenorphine depot, the development of an opioid-related behaviour scale, and a study of opioid substitution therapy uptake among chronic non-cancer pain patients. BL has also received investigator-initiated untied educational grants for post-marketing surveillance studies of opioids from Mundipharma (a tamper-resistant oxycodone formulation) and Seqirus (tapentadol). These funders had no role in the design, conduct, or interpretation of these studies. These studies were unrelated to the current DCE protocol or broader POINT study. SN has provided training around treatment of codeine dependence for which her institution received funding from Indivior.

GC reports investigator-driven untied educational grants from Reckitt Benckiser for the development of an opioid-related behaviour scale.

MC reports receiving fees from Mundipharma Limited for preparation and presentation of educational material.

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Table 1: Final attributes and levels

Attributes	Levels
Number of different medications taken on most days for pain	0, 2, 4 ,6
Known side effects of medications for pain	Mild, Moderate/Severe
Pain interference with daily activities	Never; Sometimes; Most of the time; Always
Pain care is managed by	GP only; Pain specialist; Multi-disciplinary pain management team; Myself
Risk of addiction to pain medication	Risk of 3 in 100 people or 25 in 100 people who are taking strong pain medications*
Activity goals of treatment	Able to undertake activities of daily living; Do exercises at home, including walking, most days; Participate in regular exercise classes (gym /hydrotherapy classes); Practice mindfulness regularly
Source of information on pain and pain management	None; From a doctor; By reading/ Online; From a pain management course
Out of pocket costs per month (i.e. for medications, doctor, physio or psychologist visits, or other activities you would need to pay for to help you manage your pain)	$50, 100, 200 or 300 per month

** Initial choice of four levels decreased to two after pilot study, see below*

Table2: Example of scenario

	Treatment A	**Treatment B**
Pain medications per day	2	4
Known side effects of medications	Mild	Moderate / severe
Pain interference	Never	Never
Pain care is managed by	Myself	GP only
Risk of addiction to pain medications	3 out of in 100 people	25 in 100 people
Activity goals of treatment	Do exercises at home, including walking	Do exercises at home, including walking
Source of information on pain	From my doctor	By reading/ online
Out of pocket costs per month	300	300
My choice is (please choose A or B)	☐	☐

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A protocol for a discrete choice experiment: understanding patient medicine preferences for managing chronic non-cancer pain

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A protocol for a discrete choice experiment: understanding patient medicine preferences for managing chronic non-cancer pain

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Abstract

Introduction

High rates of chronic non-cancer pain (CNCP), concerns about adverse effects including dependence among those prescribed potent pain medicines, the recent evidence supporting active rather than passive management strategies and a lack of funding for holistic programs have resulted in challenges around decision making for treatment among clinicians and their patients. Discrete choice experiments (DCE) are one way of assessing and valuing treatment preferences. Here, we outline a protocol for a study that assesses patient preferences for CNCP treatment.

Methods and analysis

A final list of attributes (and their levels) for the DCE experiment were generated using a detailed iterative process. This included a literature review, a focus group, and individual interviews with those with CNCP and clinicians who treat people with CNCP. From this process a list of attributes was obtained. Following a review by study investigators including pain and addiction specialists, pharmacists and epidemiologists, the final list of attributes were selected (number of medications, risk of addiction, side effects, pain interference, activity goals, source of information on pain, provider of pain care and out of pocket costs). Specialised software was used to construct an experimental design for the survey. The survey will be administered to two groups of participants, those from a longitudinal cohort of patients receiving opioids for CNCP and a convenience sample of patients recruited through Australia's leading pain advocacy body (Pain Australia) and their social media and website. The data from the two participant groups will be initially analysed separately, as their demographic and clinical characteristics may differ substantially (in terms of age, duration of pain, and current treatment modality). Mixed logit (MXL) and latent class (LC) analysis will be used to explore heterogeneity of responses.

Ethics and dissemination

Ethics approval was obtained from the UNSW Sydney Human Ethics committee HC16511 (for the focus group discussions, the one-on-one interviews, and online survey) and HC16916 (for the cohort). A lay summary will be made available on the NDARC website, Pain Australia's website. Peer review papers will be submitted, and it is expected the results will be presented at relevant pain management conferences nationally and internationally. These results will also be used to improve understanding of treatment goals between clinicians and those with CNCP.

Strengths and Limitations of this study

- This DCE will elucidate how people with CNCP value different treatments that include both medicines and holistic goals of pain management.
- Our DCE will be conducted in two samples: an already recruited diverse cohort of people with CNCP who have been prescribed opioids and a novel group of people with CNCP who may not have been prescribed opioids, recruited via social media.
- The samples will include the most common pain conditions such as chronic back and neck problems, arthritis and migraines.
- The study will estimate marginal willingness to pay for changes in number of medicines, level of pain interference, risk of addiction and preference of service provider.
- The preference discrete choice experiment surveys will be undertaken in Australia, which could affect generalisability to other settings.

Introduction

These are challenging times for both people with chronic non-cancer pain (CNCP) and those to whom they turn for treatment. Despite a significant increase in opioids being prescribed for CNCP in countries such as the United States, Canada and Australia[1-3] there is insufficient evidence on the long term effectiveness of use[4].

Accompanying the increase in opioid prescribing there has been a concurrent increase in harms, with more than 64,000 opioid overdoses in the US[5], 1,300 in Australia[6] in 2016 and 8,440 in Europe[7]. Responses to minimise harms associated with pharmaceutical opioids include increased regulatory controls such as prescription monitoring programs and limiting access to over-the-counter codeine in Canada, Australia, and the United States[8]. Other strategies have focused on improved clinical practice, including limiting maximum doses and prescriber education[9]. However, taken together with busy general practitioners, a shortage of pain and addiction specialists, fear of addiction and the lack of accessible and affordable alternatives for pain management this has led to increased anxiety amongst many with CNCP[10]

With chronic pain reported by approximately one-third of the US population[11] and thirty-nine percent of a representative Australian sample[12], and potential rates of dependence varying between 1% and 24% [13] among those who are prescribed potent analgesic medicines, this represents a sizable challenge.

The benefits and harms of opioids for CNCP are complex and contextual, and include factors such as age, co-morbidities, health status, type and duration of pain, concurrent medicines, patients' ability and willingness to self-manage. Under-treated CNCP adversely affects patients' wellbeing[10], but there are few data to inform the range of treatment choices available, maximise treatment outcomes and patient adherence, and minimise unintended consequences. In addition, prescribing decisions and patients' expectations are complicated by the common side effects from many medicines used in CNCP, the lack of long-term evidence on efficacy[14-17], the development of tolerance, fears of dependence and lack of funding for non-drug based treatment options.

Recent evidence suggests that active rather than passive management strategies may 'retrain the brain' to reduce pain[18], and that a multidisciplinary approach is likely to produce the most optimal outcomes, but the cost and availability of alternative treatments may affect patients' treatment choices. Additionally, cognitive behaviour therapy has been found to help patients modify situational factors and multi-modal therapies that combine exercise and related therapies with psychologically

based approaches also help reduce pain and improve function more effectively than single modalities[19-21].

Preferences of clinicians and patients can impact prescribing patterns, uptake of interventions and treatment adherence, thus affecting the effectiveness of pain management[22]. It is important to understand why some people with CNCP resort to treatments that are expensive or without evidence of efficacy; and alternatively, why some stay on opioids long-term when not experiencing clinical benefit. For example, 34% of a cohort of CNCP participants reported that there had been no clinically significant change in their activity limitations, symptoms, emotions, and overall quality of life since starting opioids[23]. Significant proportions of the cohort were using complementary or alternative interventions for their pain which have limited or no evidence of efficacy in chronic pain[23, 24]. Additionally, they often report that attending physiotherapy, specialised exercise classes or psychotherapy was often prohibitively expensive and unfunded whereas medicines and GP visits are at least partially covered by the Australian Medicare and Pharmaceutical Benefits Schemes.

The discrete choice methodology (DCE) allows for the identification of the preferences for various treatment options and potential trade-offs that individuals are willing to make. Moreover, DCEs have been widely used in the heath literature to elicit preferences from patient groups on health and non-health outcomes[25, 26]. Studies that have utilised the DCE methodology to examine patient preferences for managing CNCP have focused specifically on toleration of the adverse effects of nonselective NSAIDs and selective COX-2 inhibitors[27], management of neuropathic pain [28], surgical or non-surgical approaches for low back pain[29]; and acupuncture or infra-red treatments for low back pain[30]. These studies have often been limited to specific treatments[27-30] and to limited conditions[29, 30]. Here we outline a study protocol to elicit patient preferences for broader approaches to treatment for CNCP through use of a DCE by extending the range of attributes to encompass a wider range of treatment alternatives including holistic goals of pain management.

Aims

The aims of this study are to identify and value the factors that influence important treatment decisions among people living with CNCP, so we can better understand the choices they make. Specifically, we will assess:

1. preferences for medicines
2. impact on choice of potential side effects including the possibility of addiction;
3. willingness to pay out of pocket for preferred options, and the extent to which costs may be a barrier;

4. the extent to which having input into treatment is important; and
5. the degree to which pain interference is tolerated.

Methods and analysis

Overview of the DCE

DCEs are a method of eliciting and quantifying preferences and exploring trade-offs between the attributes (characteristics) of a treatment (or a good or service). Attribute-based DCEs permit the exploration of preferences for treatment options while varying the levels of each attribute[26, 31, 32]. DCEs are based on Lancaster's economic theory of value (1966, 1971) and presume that individuals derive utility (or well-being) not from the good itself but rather from the attributes of that good[33, 34]. They rely on an individual's knowledge or perceptions of their own preferences, and on their ability to make trade-offs between alternatives in the presence of constraints such as money, time, availability and so on.

A DCE provides respondents with several hypothetical but reasonable choice sets. Each choice set consists of at least two alternatives which comprise a set of attributes each with various levels. Respondents are then asked to choose their preferred alternative in each choice set[33]. In making a choice, the respondent identifies the alternative that yields the highest utility to them. The attributes and their levels are important, as they drive decision making. When respondents make a choice, they make trade-offs between the levels of the various attributes which can then be analysed with logistic regressions. When a cost attribute is included, it is possible to indirectly estimate willingness-to-pay (WTP) values for particular attributes of treatment [35-38]. The dependent variable in the logistic regression represents the probability of choosing one alternative with specific attributes and levels over another. The independent variables are the attributes and their levels. It is feasible to account for heterogeneity through the use of covariates in a mixed logit (MXL) or latent class (LC) models [39, 40].

Theory

Consumer theory assumes deterministic behaviour, but choice theory asserts that individual behaviour is intrinsically probabilistic (random). Individuals have a concept of the value (indirect utility) for each choice, but the researcher does not know all the factors that might affect that choice. The utility estimate consists of the knowable part and the random or unknowable parts. The random part may be due to unobserved attributes, unobserved preference variation, specification or

measurement error, or inter-individual differences in utility as a result of variation in tastes[33, 41]. The utility function in the context of the DCE can be presented as follows:

$$U_{ij} = V_{ij} + \epsilon_{ij}, j = 1.....J \quad (1)$$

Where individual i will choose alternative j if, and only if, that alternative maximises their utility amongst all *J* alternatives. The utility (U) for individual *i* is conditional on choice *j* and decomposed into explainable or systematic V_{ij} and non-explainable or random component $\varepsilon_{ij.}$ V_{ij} can be further broken down into X_{jk}, a vector of attributes of the treatment, and Z, a vector of N characteristics of the individual i, and β and γ are the respective coefficients to be estimated for K attributes, with γ_n coefficients indicating the impact that the personal characteristics have on choice[42].

$$V_{ij} = \sum_{k=1}^{K} \beta_k X_{jk} + \sum_{n=1}^{N} \gamma_n Z_{in} \quad (2)$$

where γ_{ij} is equal to 1 if alternative j is chosen, and 0 otherwise and 1 is the choice if and only if

$V_{ij} + \varepsilon_{ij} > V_{im} + \varepsilon_{im}$ for all $j \neq m$ which rearranges to

$V_{ij} - V_{im} > \varepsilon_{im} - \varepsilon_{ij.}$

Utilities are not observed, but by documenting the choices made, utilities can be estimated[43]. Additionally ($\varepsilon_{im} - \varepsilon_{ij}$) is not observed directly and so it is only possible to make observations up to a probability of occurrence with some distribution or density function. It is the choice of this distribution that affects interpretation of the probabilities [33]. Different density functions for the unobserved part of the utility ε_{ij} lead to different families of probabilistic discrete choice models.

Undertaking a DCE requires several steps including the selection of the relevant attributes and their levels, obtaining a feasible design for the DCE survey, constructing and administering the survey and determining the best-fitting model.

Patient and Public Involvement

The final survey tool (the DCE), including the framing of the question, was developed after a focus group discussion and multiple one-on-one discussions with persons who self-report as having CNCP. They were recruited from members of PainAustralia. Pain Australia is Australia's leading pain advocacy body representing the interests of a membership that includes health, medical, research and consumer organisations it works to improve the quality of life of people living with pain and to facilitate implementation of the National Pain Strategy Australia-wide. As further described below, the important constructs from this qualitative work informed the choice of attributes, levels and the

final question. A lay summary of the findings will be made available on the NDARC website and PainAustralia's website.

Determining the attributes and levels for the DCE

The selection of attributes and their levels is a key step. There is a need to balance the number of attributes to adequately describe the good or service of interest; specifying too many attributes may hinder the respondents' decision making. The number of attributes will vary with the complexity of the good being considered, but typically studies include four to eight attributes. Undertaking qualitative work to inform the selecting and framing improves the relevance and applicability of the findings[44, 45].

Focus groups and telephone interviews with people living with CNCP

As a first step in this study, a literature review was undertaken to identify the important constructs to explore in subsequent focus groups and one-on-one discussions. The intent was to recruit 20 to 25 participants to participate in focus groups, however it became apparent this was going to be difficult due to health status of participants and location. Therefore, one focus group (N=3 participants) and 13 one-on-one telephone interviews were conducted with people who had CNCP, to elicit views on topics such as: self-management, knowledge of pain mechanisms, brain plasticity, relative importance of exercise, medicines, choice of treatment provider, and barriers and facilitators to effective good treatment.

Telephone interviews with clinicians

Additionally, interviews were conducted with a range of clinicians including pain specialists, general practitioners (urban and rural), clinical nurse specialists, physiotherapists and addiction specialists (N=8). Clinician interviews elicited additional information on barriers and facilitators to treatment and views on current modalities of treatment for CNCP.

Determining the list of attributes and levels

The final list of attributes included in the DCE experiment were generated using a detailed iterative process. The first phase involved a literature review undertaken by MSh to inform the development of list of possible factors previously identified as influencing patient choice of pain treatments. This list was reviewed and further developed among the broader POINT study investigators who include pain and addiction specialists, pharmacists and epidemiologists.

These attributes developed in the first phase of the study became the basis of (a) focus group discussions with patients and (b) telephone interviews with clinicians. Two authors (MSh and GC) reviewed the recorded transcripts separately and independently analysed data thematically.

Attributes generated at this second phase included the following themes: potential side effects; concurrent medicines; necessity to work / care for others; barriers; complementary medicine; multi-modal therapies; costs; time to onset of effect; adherence/compliance; risk of addiction; co-morbidities; and self-management.

In the final phase, this broader list was reviewed by the broader POINT study investigator team, and a final list of attributes (and their levels) was agreed. Attributes (and number of levels) selected were number of medications (4), risk of addiction (4), side effects (2), pain interference (4), activity goals, source of information on pain (4), provider of pain care (4) and out of pocket costs (4).

Please insert Table 1 about here

Pilot Study

The DCE design

Having selected the attributes, levels, and number of alternatives (2), an experimental design for the survey was generated. Given the number of attributes and levels, a full factorial design including all possible combinations of attributes and their levels was not feasible. Therefore, a D-efficient experimental design that maximised model statistical efficiency by minimising the parameter standard errors was generated using Ngene[46]. The statistical efficiency of the design is improved if some prior information about these parameters is available. This can be coefficients from previous analysis or expert opinion[43, 46]. In the design for the pilot study, the prior coefficients were set to zero.

Pilot-testing attributes and levels

A pilot study was conducted among 33 people living with CNCP and who had been prescribed opioids. These data were used to refine the final list of attributes and levels. Specifically, the number of levels for the attribute 'risk of addiction to pain medicines' was decreased from 4 to 2 levels (the two extremes), as respondents did not appear to distinguish between the middle two levels. (See Table 1 for final list of attributes and levels). The pilot testing was also used assess the ease with which participants could complete the experiment: 64% reported that it was easy/very easy to complete the scenario questions, 27% found it difficult and 9% found it very difficult.

Proposed study

Significant coefficients from the pilot study data (n=33) were used in the final experimental design. An efficient design of 80 scenarios, with 10 blocks was generated for the final design (each participant will be presented with one block of eight scenarios). See Table 2 for an example of a scenario.

Please insert Table 2 about here

Participants and survey procedures

There is no agreement on the correct sample size required for a DCE[47]. However, research has shown that in all DCE studies with efficient designs, model estimate precision increases rapidly at sample sizes greater than 150 and then flattens out at around 300[48]. It is also estimated that a minimum sample size of 200 respondents per sub-group be used for studies involving an analysis of differences between samples[49]. The proposed DCE will be administered to two groups of participants (see below) with the sample size of each group being 200 participants or greater. To examine the possibility of different treatment preferences in people living with CNCP we included two distinct groups. The POINT cohort consist of participants who have been prescribed opioids for CNCP and have been on long-term opioids for an average of seven years at the time of the current study. The other sample includes CNCP recruited online. These participants are not necessarily prescribed opioids and we will examine the differences in treatment preferences between people prescribed and not prescribed opioids for CNCP.

Each participant will be randomly allocated to one of ten blocks with each block having eight DCE questions. In addition to the DCE questions, a range of demographic and covariates will be collected (i.e. age, gender, education, marital status) clinical characteristics (duration of pain, number and type of medicines, pain interference scores).

(i) Pain and Opioids IN Treatment (POINT) prospective cohort study

The first source includes participants in POINT study, a national prospective cohort of 1,514 people living with CNCP [23]. The POINT study, currently in its fifth year, recruited participants through community pharmacies across Australia. Participants when recruited were: 18 years or older; living with CNCP (defined as pain lasting longer than three months); taking prescribed Schedule 8 opioids (including morphine, oxycodone, buprenorphine, methadone and hydromorphone) for CNCP for greater than six weeks when recruited; competent in English; mentally and physically able to participate in telephone and self-complete interviews; and did not have any serious cognitive impairments, as determined by the interviewer at the time of screening. The POINT cohort

participants are interviewed annually over the phone, and the DCE survey will be included as part of the fifth-year interview. Participants in the POINT cohort study will be invited to participate in the survey and reasons for not participating will be recorded; the first consecutive 33 interviews of the fifth-year interview were administered the pilot study questionnaire and these participants will not complete a second DCE. The DCE will be mailed to participants prior to the date of interview along with an explanation of the study aims and consent forms. The DCE questionnaire will then be completed by the POINT interviewers over the phone as part of the regular POINT interview schedule. Covariates for the DCE will be drawn from baseline line data and the most recent interview.

(ii) Online survey of people living with CNCP

A second group of respondents will be recruited on-line through Pain Australia, a national peak body and pain advocacy organisation and through social media. This group will be asked to complete an identical DCE survey on-line (via Qualtrics, hosted at UNSW Sydney), plus selected demographic, pain characteristics, type of medicines questions drawn from the POINT survey. Similar to the POINT cohort, participants who are eligible for the online survey will be aged 18 years or older, reside in Australia, and are living with CNCP (defined as pain lasting longer than three months). Unlike the POINT cohort, however, the online sample will not be required to have been prescribed Schedule 8 opioids (although this is not an exclusion in the online survey).

Links to the online survey will be posted on the Pain Australia website, the National Drug and Alcohol Research Centre website, and their associated Facebook pages, and twitter feeds. Recruitment will continue for four months (or until the current round of interviews of the cohort are complete) with the objective of achieving at least 200 surveys completed online. Respondents will be randomly allocated one of the ten blocks, and demographic and covariates will match collected from the POINT cohort.

Data analysis

The data from the two participant groups will be initially analysed separately, as their demographic and clinical characteristics may differ substantially (in terms of age, duration of pain, and current treatment modality). The analysis of the DCE responses will be analysed using Nlogit software[46]. Initially a multinomial logit model will be used. Mixed logit (MXL) and latent class (LC) analysis will be used to explore heterogeneity of responses. Number of medicines, and out-of-pocket costs will be treated as continuous variables; all categorical variables will be effects coded which means the

constant will not be confounded with the grand mean and coefficients for base levels can be estimated[50].

Tables of coefficients for the levels and covariates will be presented with relevant statistical measures including pseudo r-squared, log likelihood test, and the AIC to test for goodness of fit of the model. In addition, the marginal rate of substitution (the negative ratio between any two estimated coefficients) will be calculated. This will allow policy makers and clinicians to understand the relative importance of different attributes, and the respondents' willingness to give up some amount of one attribute in order to obtain more of another.

Article Summary

Strengths and Limitations of this study

The DCE approach offers great potential for informing clinicians as to patient preferences for pain management. Where preferences do not align with current evidence, the findings will provide an opportunity to develop strategies for improving knowledge. If preferred options are those that are known to be effective but also more expensive for the patient, the results can be used to inform policy makers. However, there are methodological limitations that are common to all DCEs. In our study, one challenge was to select attributes and levels that both reflect treatment for CNCP and outcomes but result in a practical number to include. Our choice to use eight attributes likely places higher cognitive demand on respondents but we sought to mitigate this by only requiring each person to complete eight DCE choices.

Our DCE will be conducted in a large, diverse sample of people living with CNCP, including the most common pain conditions such as chronic back and neck problems. This DCE differs from previous studies in that it will elucidate how people value different CNCP treatments, not just medicines or not just surgery. This study will also permit the estimation of the marginal willingness to pay for different treatment options and outcomes. Although the marginal willingness to pay for preferred attributes will assist policy makers generally, some of the results may not be generalizable to resource-poor settings or countries without universal healthcare systems.

Ethics and dissemination

Ethics approval was obtained from the UNSW Sydney Human Ethics committee HC16511 (for the focus group discussions, the one-on-one interviews, and online survey) and HC16916 (for the POINT cohort). A lay summary of the findings will be made available on the NDARC website and Pain Australia's website. Peer review papers will be submitted, and it is expected the results will be presented at

relevant pain management conferences nationally and internationally. These results will also be used to improve understanding between clinicians and those with CNCP of goals of treatment.

Consent

Written consent was obtained from those who attended the focus groups and verbal consent was obtained from those who volunteered for phone interviews (researchers were only aware of first name of telephone participants). Consistent with UNSW ethics, for the on-line DCE survey, consent was implicit in the decision to complete the survey after reading the participation information sheet. For the POINT cohort, consent has previously been obtained from participants and the DCE is part of the scheduled interview.

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Author Contributions

MSh was lead author and responsible for the study design, conducted the qualitative interviews and analysis, and the writing of the paper. GC and BL were involved qualitative interviews and its analysis. MSch contributed to the survey development and administration of the survey. MSh, BL, SN, MC and GC were involved in defining and selecting the attributes and levels. All authors provided detailed input to the paper.

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Competing interest statement

MSh and MS – nil

BL and SN report investigator-driven untied educational grants from Reckitt Benckiser/Indivior for studies of buprenorphine-naloxone and buprenorphine depot, the development of an opioid-related behaviour scale, and a study of opioid substitution therapy uptake among chronic non-cancer pain patients. BL has also received investigator-initiated untied educational grants for post-marketing surveillance studies of opioids from Mundipharma (a tamper-resistant oxycodone formulation) and Seqirus (tapentadol). These funders had no role in the design, conduct, or interpretation of these studies. These studies were unrelated to the current DCE protocol or broader POINT study. SN has provided training around treatment of codeine dependence for which her institution received funding from Indivior.

GC reports investigator-driven untied educational grants from Reckitt Benckiser for the development of an opioid-related behaviour scale.

MC reports receiving fees from Mundipharma Limited for preparation and presentation of educational material.

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Table 1: Final attributes and levels

Attributes	Levels
Number of different medications taken on most days for pain	0, 2, 4 ,6
Known side effects of medications for pain	Mild, Moderate/Severe
Pain interference with daily activities	Never; Sometimes; Most of the time; Always
Pain care is managed by	GP only; Pain specialist; Multi-disciplinary pain management team; Myself
Risk of addiction to pain medication	Risk of 3 in 100 people or 25 in 100 people who are taking strong pain medications*
Activity goals of treatment	Able to undertake activities of daily living; Do exercises at home, including walking, most days; Participate in regular exercise classes (gym /hydrotherapy classes); Practice mindfulness regularly
Source of information on pain and pain management	None; From a doctor; By reading/ Online; From a pain management course
Out of pocket costs per month (i.e. for medications, doctor, physio or psychologist visits, or other activities you would need to pay for to help you manage your pain)	$50, 100, 200 or 300 per month

** Initial choice of four levels decreased to two after pilot study, see below*

Table2: Example of scenario

	Treatment A	**Treatment B**
Pain medications per day	2	4
Known side effects of medications	Mild	Moderate / severe
Pain interference	Never	Never
Pain care is managed by	Myself	GP only
Risk of addiction to pain medications	3 out of in 100 people	25 in 100 people
Activity goals of treatment	Do exercises at home, including walking	Do exercises at home, including walking
Source of information on pain	From my doctor	By reading/ online
Out of pocket costs per month	300	300
My choice is (please choose A or B)	☐	☐