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*Published in:*  
British Journal of General Practice

*DOI:*  
[10.3399/bjgp19X707369](https://doi.org/10.3399/bjgp19X707369)

**IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.**

*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2020

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Bekhuis, E., Gol, J., Burton, C., & Rosmalen, J. (2020). Patients' descriptions of the relation between physical symptoms and negative emotions: a qualitative analysis of primary care consultations. *British Journal of General Practice*, 70(691), E78-E85. <https://doi.org/10.3399/bjgp19X707369>

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## Patients' descriptions of the relation between physical symptoms and negative emotions:

a qualitative analysis of primary care consultations

### Abstract

#### Background

Primary care guidelines for the management of persistent, often 'medically unexplained', physical symptoms encourage GPs to discuss with patients how these symptoms relate to negative emotions. However, many GPs experience difficulties in reaching a shared understanding with patients.

#### Aim

To explore how patients with persistent symptoms describe their negative emotions in relation to their physical symptoms in primary care consultations, in order to help GPs recognise the patient's starting points in such discussions.

#### Design and setting

A qualitative analysis of 47 audiorecorded extended primary care consultations with 15 patients with persistent physical symptoms.

#### Method

The types of relationships patients described between their physical symptoms and their negative emotions were categorised using content analysis. In a secondary analysis, the study explored whether patients made transitions between the types of relations they described through the course of the consultations.

#### Results

All patients talked spontaneously about their negative emotions. Three main categories of relations between these emotions and physical symptoms were identified: separated (negation of a link between the two); connected (symptom and emotion are distinct entities that are connected); and inseparable (symptom and emotion are combined within a single entity). Some patients showed a transition between categories of relations during the intervention.

#### Conclusion

Patients describe different types of relations between physical symptoms and negative emotions in consultations. Physical symptoms can be attributed to emotions when patients introduce this link themselves, but this link tends to be denied when introduced by the GP. Awareness of the ways patients discuss these relations could help GPs to better understand the patient's view and, in this way, collaboratively move towards constructive explanations and symptom management strategies.

#### Keywords

communication; consultation; emotions; medically unexplained symptoms; relation.

### INTRODUCTION

Persistent physical symptoms are prevalent in the general population and are associated with reduced quality of life.<sup>1-3</sup> Although these symptoms are often referred to as medically unexplained, they are increasingly recognised as representing complex interactions between peripheral and central processes.<sup>4,5</sup> The management of the symptoms includes a combination of physical and psychological elements,<sup>6</sup> and is often perceived as challenging by both patients and GPs.<sup>7,8</sup> Patients highly value care that addresses the breadth of biopsychosocial aspects.<sup>9,10</sup>

One element of the management of persistent physical symptoms focuses on negative emotions.<sup>2,11</sup> These emotions have the potential to play a part in worsening or maintaining physical symptoms, in addition to being a response to the symptoms.<sup>4,12</sup> Furthermore, patients with physical symptoms as well as negative emotions report more functional and social limitations than patients without these emotions.<sup>1</sup> Therefore, primary care guidelines recommend that GPs address the relation of these negative emotions with symptoms.<sup>11,13,14</sup> Nevertheless, many GPs experience difficulties in arriving at a shared understanding with patients about this relation.<sup>15-17</sup> In particular, when GPs introduce inappropriate or premature

psychosocial links, these are typically rejected by patients.<sup>15,16,18,19</sup> It has been suggested that this tension is related to the embedding of 'medically unexplained symptoms' in psychiatric rather than somatic classification systems, and this dualism leads patients to feel that the legitimacy of their symptoms is under threat.<sup>17</sup>

Several authors have proposed that a shared understanding about the relation between symptoms and emotions should be formed while using the patients' starting point as a basis.<sup>13,20-22</sup> In a process of constantly seeking agreement and adjusting explanations, the GP and patient can collaboratively broaden the conversation to other types of relations and, as such, formulate rich explanatory models.<sup>13,20,22</sup> However, despite the existence of theoretical models that refer to thought patterns of patients regarding the relation between physical symptoms and emotions,<sup>20</sup> the authors were unable to find a classification of how patients describe it in consultations.

This study aimed to classify the types of relations between physical symptoms and emotions that patients describe in primary care consultations. A secondary aim was to examine if patients moved between types of relations over time, to examine if the classification can be used to monitor a change in their presentation

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**Submitted:** 10 February 2019; **Editor's response:** 3 April 2019; **final acceptance:** 3 June 2019.

#### ©British Journal of General Practice

This is the full-length article (published online 17 Dec 2019) of an abridged version published in print. Cite this version as: **Br J Gen Pract 2019;** DOI: <https://doi.org/10.3399/bjgp19X707369>

## How this fits in

Primary care guidelines for managing persistent 'medically unexplained' physical symptoms recommend discussing the links between physical symptoms and negative emotions. When GPs propose these links, patients often find them unhelpful or actively block them. This study examined patients' own descriptions of the links between physical symptoms and negative emotions, and found that patients articulated three types of associations: separated (negation that symptom and emotion were related); connected (symptom and emotion were presented as distinct but connected entities); and inseparable (symptom and emotion were combined within one entity). Understanding how patients describe associations between physical symptoms and negative emotions may help GPs to find common ground for communication and enable appropriate symptom management strategies to be constructed.

during interventions. A qualitative analysis was conducted of a series of extended consultations with specially trained GPs for patients with multiple persistent physical symptoms.<sup>14</sup>

## METHOD

### Data source

For the current study, data from the Multiple Symptoms Study 1 and 2<sup>14,23</sup> were extracted. These studies focused on the effects of a consultation intervention in primary care for patients with multiple persistent physical symptoms. This intervention, consisting of three to four consultations of 20–40 minutes with trained GPs, aimed to reduce the intensity and impact of symptoms.<sup>14,23</sup> GPs were instructed to explore emotions when openings were presented by the patient, rather than to impose their own ideas upon the patient. Furthermore, they were encouraged to consider emotions as parallel processes that can be connected to physical symptoms, rather than presenting them as the sole cause or label of symptoms. In both studies, patients were identified through a clinical database search in their usual GP practice and the completion of the Patient Health Questionnaire-15 (PHQ-15; or its shortened 14-item version) to assess the severity of physical symptoms.<sup>24</sup> Patients were eligible for inclusion if they had a diagnostic code in the clinical database for one or more functional somatic syndromes, had been referred to specialists at least two times in the preceding 3 years, and had a

PHQ-15 score of  $\geq 10$ . At study entry, patients filled in the Patient Health Questionnaire-9 (PHQ-9) and the Generalised Anxiety Disorder-7 (GAD-7) to assess depressive and anxiety symptoms, respectively.<sup>24,25</sup>

### Data analysis

**Selection of consultations.** All 112 consultations with 39 patients in which the intervention was delivered were audio-taped and transcribed verbatim. Patients were purposively sampled based on key variables (that is, age, sex, baseline scores on the PHQ-15, PHQ-9, and GAD-7, and the treating GP) to maximise variation. As one aspect of the study was the transition between different types of relations through the course of their consultations, patients who completed at least three consultations were particularly focused on. The analyses began on a subset of 12 patients and aimed for saturation defined as being no new insights on types and characteristics of categories gained in three sequentially analysed patients. As the inclusion of three additional cases did not provide additional insights, the final sample constituted 15 patients (Table 1).

### Analysis method

First, patients' accounts of negative emotions were coded in line with methods used in previous studies.<sup>26,27</sup> These accounts were defined as explicit and verbal expressions of a negative emotional state. Implicit accounts of emotions (for example, a situational description of a distressing event such as a conflict without explicitly describing an emotion) were excluded to avoid imputation of the patient's narrative by the researchers. Descriptions were interpreted in the context of the conversation and while listening to the intonation of the patient. Specific attention was paid to words or phrases with multiple definitions, for example, 'stress' can refer to external stressors as well as an internal state characterised by worry or agitation, and 'I was like: oh my God!' may refer to a positive and negative emotion. Such quotations were included only when it could be inferred with confidence that the patient was referring to a negative emotion. Accounts were categorised based on the type of emotion they concerned with open coding, and names of the categories were formulated while staying true to the words most often used by patients.

In a second step, all quotes in which patients described a relation between a negative emotion and physical symptom were selected. To stay true to the patient's intent, only relations that were semantically specified were considered (for example, 'I

**Table 1. Sample characteristics**

Patient number	Age in category, years	Sex	Main physical symptoms	PHQ-15 score	PHQ-9 score	GAD-7 score	Number of consultations	GP number
<b>Multiple Symptoms Study 1</b>								
1	35–49	F	Fatigue, musculoskeletal pain	13	6	2	4	1 (male, >15 years of experience)
2	50–64	M	Musculoskeletal pain, fatigue, headache	15	10	6	4	1
3	35–49	F	Fatigue	16	12	20	4	1
4	50–64	F	Musculoskeletal pain and weakness	13	21	18	1	1
<b>Multiple Symptoms Study 2</b>								
5	20–34	F	Gastrointestinal symptoms, fatigue, headache	12	11	14	4	2 (female, >15 years of experience)
6	35–49	F	Musculoskeletal pain, gastrointestinal symptoms	11	2	1	2	2
7	50–64	F	Gastrointestinal symptoms, musculoskeletal pain, excessive perspiration	16	4	1	4	2
8	35–49	F	Gastrointestinal symptoms, musculoskeletal pain	13	4	3	3	3 (female, >15 years of experience)
9	35–49	F	Musculoskeletal pain, balance problems, headache	28	20	19	4	3
10	≥65	F	Fatigue, headache	10	3	2	4	3
11	35–49	F	Palpitations, gastrointestinal symptoms	19	3	8	1	4 (male, <5 years of experience)
12	20–34	F	Musculoskeletal pain and weakness	15	12	5	3	4
13	50–64	M	Musculoskeletal pain, 'heart trouble' (breathlessness, lump in throat)	18	16	12	3	4
14	50–64	M	Musculoskeletal pain, gastrointestinal symptoms	12	13	9	3	5 (female, >15 years of experience)
15	35–49	F	Musculoskeletal pain, headache, tinnitus	15	5	0	3	5

GAD-7 = Generalised Anxiety Disorder-7. PHQ-9 = Patient Health Questionnaire-9. PHQ-15 = Patient Health Questionnaire-15.

feel down because of the pain'). In addition, it had to be clear that the relations included a negative emotion as well as a physical symptom; terms at the interface (for example, 'feeling tense') were excluded if their meaning could not be inferred from the conversation. The quotes were analysed with conventional content analysis.<sup>28,29</sup> Using a one-sheet-of-paper (OSOP) method, quotes were written on one document and rearranged by looking at similarities and differences to form categories inductively.<sup>30</sup> To explore whether patients showed a transition in their presentation of categories through the course of their consultations, a secondary analysis was performed. Each patient's pattern of category use over time was analysed, and switches from one category to another while describing a specific situation were searched for.

Coding was done in ATLAS-ti 8 and first performed independently and then compared by two of the authors (EB and JG). The analysis was done by these researchers together and differences were discussed until agreement was reached. In order to ensure intersubjective reproducibility and comprehensibility, the analysis was regularly referred to senior researchers who specialised in persistent physical symptoms (CB and JR).

## RESULTS

All patients described some negative emotions, but the number of instances differed considerably across patients (ranging from 3–21). Six categories of emotions were identified: anxiety, frustration, low mood, embarrassment, guilt, and other emotions that could not be fitted into these categories (Table 2). Patients who disclosed fewer emotions were generally less talkative and more focused on the physical aspects of their symptoms. Typically, patients presented the first emotion within 5 minutes of the start of the first consultation, and the frequency of occurrence decreased as the intervention progressed. In most quotes, patients related the emotion to physical symptoms (the amount ranged from 1 to 16 times). Patients initiated most descriptions of relations themselves, with the remainder in response to questioning and sometimes prompting by the GP. Spontaneous descriptions were more detailed than those occurring after a question from the GP. Some patients, particularly those going through major life events, tended to describe emotions without referring to their relation with their physical symptoms. They elaborated on emotions in the context of external stressors or questioned if the emotion was

**Table 2. Categories of emotions**

Category	Examples of emotions within category	Number of quotes referring to category of emotions <sup>a</sup>
Anxiety	Anxiety Worry Panic Nervousness	69
Frustration	Frustration Annoyance Anger Irritation	49
Low mood	Depression Sadness Weariness Feeling down	47
Embarrassment	Embarrassment Shame Feeling humiliated Feeling mortified	19
Guilt	Guilt	1
Symptoms that could not be fitted into specific category	Emotional crisis Feeling overwhelmed Feeling stressed out	64

<sup>a</sup>One quote could refer to emotions from multiple categories.

part of an affective disorder. The pattern in which patients presented emotions or their relation with physical symptoms (that is, number of times, types of categories, at which stage of the intervention) was not clearly related to the patients' sex or age, nor the severity of somatic, depressive, and anxiety symptoms.

**Categories of relations between negative emotions and physical symptoms**

Three main categories of relations between negative emotions and physical symptoms were identified: separated, in which a link between the symptom and emotion was negated; connected, in which the symptom and emotion were presented as related but distinct entities; and inseparable, in which the symptom and emotion were combined within a single entity (Table 3).

*Separated.* In the separated category, patients explicitly negated a link between a symptom and an emotion. Characteristic for this category was that the negation concerned a relation in which the physical symptom was fully caused by or attributed to an emotion, and emotional labels like 'depression' or 'anxiety disorder' were used. Patients used the category during various stages of the intervention and frequently indicated that they believed the relation to be true in general, but that they had not experienced it themselves:

*'They looked at all the obvious signs because, I mean, they tested me physically, but they also looked at me emotionally as well, which is understandable. But I wasn't going through any great emotional crisis and I wasn't depressed and I wasn't stressed and I have ... I don't know how most people work, but I'm a very strong faith so it keeps me sane, so I wasn't ... I would've told them if I was depressed and I wasn't, so **there wasn't an emotional trigger.**'* (Patient [P] 12, female [F], age 20–34 years)

Some patients negated in a tense or angry way a relation suggested by a physician in which symptoms were caused by or attributed to emotions:

**GP:** *'They [pain and fatigue] are closely linked in with emotions and how all of that works, so being upset, being stressed, being angry.'* (GP4)

**Patient (P):** *'Yeah, correlation between sad feelings and pain. I get it.'* (P12, F, age 20–34 years)

**GP:** *'So it starts to hold you back and you can get into a little bit of a cycle here.'*

**P:** [starts crying and says angrily] *'A rut, yeah, I appreciate that. But then if you couldn't do half the things you wanted to do, you would feel overwhelmed and stressed out. **But that's not why I'm sore.**'*

*Connected.* The connected category included descriptions of a symptom and an emotion as distinct, yet related entities. This category included confidently presented statements that could lead to the identification of targets for management strategies. It was found during all stages of the intervention with all patients. Connections were subdivided into two types: a) isolated connection; and b) vicious circle.

In isolated connections, the symptom and the emotion either unidirectionally influenced each other or were linked in time. Typically, patients briefly described regularly experiencing the emotion as a consequence of the symptom, and in this way seemed to wish to underline the impact of the symptom on their daily life:

*'I still have this massive sweating, it's a current one, **it's just very, very annoying, embarrassing, frustrating, depressing.**'* (P7, F, age 50–64 years)

**'Me stressing about her** [patient's sister] **makes me not well.** So I kind of have to go

**Table 3. Categories of relations between physical symptoms and emotions**

Category	Type of relation	Number of quotes referring to		Characteristics			
		category of relation	Content	Form	Initiation	Category of emotions	Stage of intervention
<b>Separated</b> The physical symptoms and emotions are distinct entities that are unrelated	<b>Negated relation</b>	12	Physical symptom is not caused by or attributable to emotion	Negation of (a previous) physician's suggestion, sometimes while expressing anger	Introduced by patient, emotions are spontaneous or in response to GP's suggested relation	Anxiety Low mood	Any
<b>Connected</b> The physical symptoms and emotions are distinct entities that are related	<b>a) Isolated connection</b>	87	Cause-effect relation regularly experienced	Short statements that are frequently repeated throughout the consultation	Spontaneously introduced by patient	Frustration Embarrassment Anxiety	Any
	<b>b) Vicious circle</b>	11	Complex vicious circle underlying symptom	Brief confirmation of GP's suggested relation	Introduced by GP, adopted by patient	Anxiety	Middle
<b>Inseparable</b> The physical symptoms and emotions are combined within a single entity	<b>a) Integrated whole</b>	11	Attribution of physical symptom to affective disorder	Exploratory narrative	Spontaneously introduced by patient	Anxiety Low mood	Start
	<b>b) Fragments of a whole</b>	8	Distressing state with physical and emotional aspects	Chaotic narrative	Spontaneously introduced by patient	Anxiety	Start

— well, not I don't care — but if **it is making me ill to stress about her**, then I have to say: I'm just not going to. (P4, F, age 50–64 years)

A vicious circle referred to a sequence of reciprocal cause and effect in which a symptom and an emotion intensified the effect of each other. Most patients described vicious circles after they had been introduced by the GP by briefly confirming the suggested relation (*'the pain ... a little bit better'*). However, a few patients, particularly those who described complex biopsychosocial explanations for their symptoms, spontaneously introduced vicious circles:

*'The pain, the heart things that you're describing, and the shortness of breath, there's no doubt to my mind that those are complicated processes at play. And everything that's bad and making you feel depressed and making you feel down, that's going to be filtering down, and making things worse. So that's a vicious circle really, isn't it?'* (GP4)

**'That's right, one that needs to be broken.** How I don't know, I really don't know.' (P13, M, age 50–64 years)

*'I think that naturally leads us on to thinking about how we can make things a little bit better.'* (GP4)

*'The headache adds to making me also tired because **it wears you down**. It's not a — you know when you've got really bad headache that you go away and you get a paracetamol because it's an ache — it's not a throb. It's just a continuous there dullness **that wears you down, and when I get really tired, it starts to get quite bad**. That's more of a stabbing pain.'* (P1, F, age 35–49 years)

**Inseparable.** Patients described a symptom and an emotion as combined within one entity in the inseparable category. This category was typically exploratory, included metaphors, and was introduced by patients at the beginning of the intervention. The symptom and emotion could be presented in two ways: an integrated whole, or fragments of a whole.

In descriptions of an integrated whole, the symptom and emotion were presented as one entity (that is, the symptom was part of the emotion or vice versa) (*'One night towards the end ... pain of the brain'*). This category concerned an exploration of the source of the symptom, which was typically an affective disorder:



*'I've been on a heart monitor and everything, but they haven't come up with anything, so whether it's a psychological thing or just some kind of panic attack?' (P11, F, age 35–49 years)*

Most patients referred to their previous experiences with affective disorders:

*'At one stage I just thought: is it depression again? Because I've been through it before.'* (P3, F, 35–49 years).

*'One night towards the end I woke up at 2.15 with this problem that's been harassing me for the last 2 years with my sister. And because of the meditation it was bringing it up. I had such a pain in my head with it, the worry was very painful. And so I sat on the end of the bed and started to do the "scanning of the body"-meditation, and eventually overcame the pain of the brain.'* (P11, F, age 35–49 years)

In the 'fragments of a whole' category, patients described the symptom and the emotion as inseparable features of an experience. The quotations included a chaotic narrative of a distressing state and patients were searching for the right words to describe it. The quotations were part of an active process of trying to understand the nature of the experience:

*'The bit I can't work out is that I can just physically function all day and at some point it's like I just ... It's like a wall hits me and it's ... And you can physically, I've been told you can physically ... And I know that it's hit me. I've been fine or I've been a bit tired all week, but Sunday night it was ... I wasn't doing anything and the wall hit me and I just ... it's like I just ... I can't cope with it. I can't cope with anything and I have ... it just ... it's like a ... it's like the ... just the fatigue engulfs me.'* (P1, F, age 35–49 years)

### Transitions between categories

In a secondary analysis, the study explored whether patients could make a transition from one category to another through the course of their consultations. It was found that three patients presented one category, 11 described two or three categories, and one patient described five categories of relations.

However, most patients who described multiple categories referred to varying symptom–emotion combinations or contexts and therefore did not necessarily show an obvious change in their presentation during the intervention. Four instances

were identified in which a patient showed an obvious transition in the presentation of a specific situation. This number was not sufficient to describe transitional patterns in detail.

In general, these transitions occurred in a dialogue in which the patient and GP negotiated novel types of relations. Two patterns of category switches were encountered: from a separated to an isolated connection; and from isolated connection to a vicious circle.

In the following quotes, the patient (P13, M, age 50–64 years) first describes an isolated connection, and later expands this, encouraged by the GP (GP4), to a vicious circle:

**GP:** *'And how are you feeling about all this [the pains], just as you are just now?'*

**P:** *'Well depressed. What else can I say. I don't know, just depressed, just feel like I'm getting nowhere.'*  
[...]

**GP:** *'And can you see that they [these feelings] might be feeding back and, and making the symptoms worse as well?'* (GP4)

**P:** *'Possible, yes, very possible. That's what I'm saying, my head's maybe playing with my mind. My mind's probably playing with me, making things worse. I work myself up, I get worse.'*

## DISCUSSION

### Summary

This study showed that patients with persistent physical symptoms describe different types of relations between symptoms and emotions. Relationships constituted three main categories: separated (negation of a link), connected (the physical symptom and the emotion are two linked entities), and inseparable (the physical symptom and emotion are combined within one entity). Some patients moved from one category to another through the course of their consultations.

### Strengths and limitations

The strengths of this study are the dual independent coding and discussing of the analyses in a multidisciplinary team from general practice, psychiatry, and psychology.<sup>30</sup> Furthermore, the study stayed true to the patients' intent by focusing on explicit descriptions of emotions and their relation with physical symptoms. A limitation of this approach is that there may be some accounts that were missed where patients

made implicit notice of emotions and/or relations; for example, by using terms at the interface of the physical and emotional (such as, *'tense'*).<sup>27</sup> Additionally, although terms referring to physical or emotional aspects were inferred while staying as true as possible to the intent of the patient, it should be noted that this distinction is a simplification of the complex biopsychosocial reality.

Ambiguity with respect to the conceptual embedding of symptoms was extensively discussed before quotes were subjected to further analysis. Data were, however, derived from extended primary care consultations with specially trained GPs and not typical short GP consultations of 10 minutes. Although these long consultations were more likely than short consultations to include discussions involving the relation of physical symptoms with negative emotions, the passages of discussions were brief and so compatible with 'ordinary' consultations. Finally, as the study identified only four instances of clear transitions in patients' use of categories over time, it was not possible to study their pattern in detail. Still, that such transitions occurred confirms that the categories can be used in future studies; for example, to identify interactional patterns related to transitions in patients' presentations with conversation analysis.<sup>31</sup>

#### Comparison with existing literature

The finding that patients frequently present their emotions in primary care consultations is in line with previous studies.<sup>32-35</sup> Although this study was the first to systematically assess the types of relations patients present in primary care consultations, other studies have indicated that many patients with persistent physical symptoms present their symptoms dualistically by negating a relation with emotions.<sup>18,19,36</sup> Interestingly, in these studies the GPs primarily used classic psychological reattribution techniques,<sup>18,36</sup> which centralise the assignment of emotional causes or labels to symptoms.<sup>37</sup> This study found that patients forcibly rejected this in the separated category,<sup>18,36</sup> suggesting that patients may primarily use dualistic expressions in response to reattribution by the GP. It has been reported before that many patients find reattribution too simplistic and stigmatising.<sup>9</sup> This could partly explain the limited efficacy of interventions based on reattribution for persistent physical symptoms.<sup>11,38,39</sup> Nevertheless, some patients in this study openly explored the possibility that their symptoms were part of an affective disorder in the inseparable category. This

could indicate that patients can and do acknowledge emotional attribution or labels when they introduce them themselves, but tend to disagree when they are imposed upon them by the GP.<sup>20</sup>

#### Implications for practice

The results of this study have several implications for the care of patients with persistent physical symptoms. First, that patients spontaneously presented emotional states of anxiety, frustration, low mood, and embarrassment as well as guilt indicates the importance of considering a broad spectrum of emotions in consultations for persistent physical symptoms. However, clinical guidelines for the management of persistent physical symptoms encourage GPs mainly to concentrate on the narrow field of depressive and anxiety disorders,<sup>12,40,41</sup> and a similar focus is adopted in screening instruments.<sup>24,25,42</sup> As all patients in this study, irrespective of the severity of their depressive and anxiety symptoms, frequently presented emotions, the findings stress the importance of picking up on patients' emotional cues and encouraging patients to elaborate on them.

Interestingly, the study found that patients tended to disclose fewer emotions as the intervention progressed. This might be related to the structure of the intervention, which gradually shifted the focus from symptom exploration to the creation of symptom management strategies. As the GP's role became increasingly more dominant in the follow-up consultations to create such strategies, the space for the patient was naturally reduced. This indicates that, in ordinary consultations aimed at exploring the problem space, it is essential for GPs to create an open conversation in which they actively listen to and collaborate with the patient.<sup>43</sup> Allowing patients the space to arrive at explanations themselves rather than imposing it on them could also help to create richer explanatory models,<sup>20,44</sup> as relations that were mentioned spontaneously by patients were presented in more detail than those in response to directive questions and prompting by the GP.

Patients with persistent physical symptoms present a wide variety of negative emotions in extended primary care consultations. In contrast with previous research suggesting that patients have dualistic presentations, this study found that patients do not only separate emotions from physical symptoms, but also describe them as entities that are connected to, or inseparable from, these symptoms.

#### Funding

The Multiple Symptoms Study 1 and 2 were funded by the Chief Scientist Office (reference CZG/2/412 and CZH/4/495).

#### Ethical approval

The Multiple Symptoms Study 1 and 2 were approved by the Lothian Research Ethics Committee (reference 09/S1102/34) and the North East Scotland Ethics Committee (reference 14/NS/1014);<sup>14,23</sup> these approvals also included a detailed analysis of the consultations as conducted in the current study. All participants gave informed consent.

#### Provenance

Freely submitted; externally peer reviewed.

#### Competing interests

The authors have declared no competing interests.

#### Acknowledgements

The authors would like to thank Inge Stortenbeker for sharing her expertise during the course of this research and Rachel Grob for sending relevant literature about the analysis method.

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