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The impact of herpes zoster and subsequent chronic pain on patients' daily lives

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Title: The impact of herpes zoster and subsequent chronic pain on patients' daily lives

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Corresponding Author: Dr Benoit Arnould,

Corresponding Author's Institution: Mapi Values

First Author: Benoit Arnould

Order of Authors: Benoit Arnould; Khadra Benmedjahed, BA; Jean-Luc Gallais, MD; Patrick Giniès, MD; Ralf Baron, MD

Abstract: Aim: The aim of our study was to carry out a literature review and develop a model illustrating the domains of patients' lives that are impacted by herpes zoster (HZ) and subsequent chronic pain.

Subject and Methods: Biomedical databases and online congress archives were searched using keywords related to HZ or post-herpetic neuralgia (PHN) and social, psychological or physical impact. 733 abstracts were reviewed. 29 publications containing concepts reported by patients were retained for the model. Wilson and Cleary's Model was used to organise the findings. Links between concepts were documented on three levels; hypothesis, observation and evidence. The final model illustrates the concepts impacted by HZ and PHN, relationships between these concepts and the level of evidence identified.

Results: The concepts identified from the articles were grouped into the following categories: Biological/Physiological, Symptom Status, Functional Status, Health Perceptions, Characteristics of the Individual, Health-Related Quality of Life (HRQOL), Treatment and Characteristics of the Environment. Evidence exists that HZ-related pain directly impacts Functional Status, Health Perceptions and HRQOL. Conclusion: Patients report that all major domains of life are impaired by HZ or subsequent chronic pain. HZ and its painful and debilitating complications can have a substantial impact on physical, psychological, social and role functioning, HRQOL and activities of daily living. The impact on elderly patients needs to be further assessed with appropriately designed and validated instruments, with specific attention paid to dependence.

Response to Reviewers: Lyon, 30 March 2010

Wilhem Kirch
Editor-in-chief, Journal of Public Health

Ref: Ms. No. JOPH-D-09-00070, "The impact of herpes zoster and subsequent chronic pain on patients' daily lives"

Dear Editor,

Thank you and the reviewers for your feedback on our manuscript, "The impact of herpes zoster and subsequent chronic pain on patients' daily lives".

Attached is our revised manuscript based on the reviewers' comments: we joined a version of the manuscript with track changes, and the manuscript with these changes accepted. Below we provide our point-by-point responses to these comments.

Reviewer #1:

"Herpes zoster and the painful complication PHN have a severe impact on patient's quality of life. Due to the actual discussion on the prophylaxis of VZV, I really sympathize with this very good review of the literature. Although the mass of information provided is difficult to digest, it is really helpful for the present discussion. This manuscript helps to have hard data in a subject which we already seem to know; this review puts the focus on the complications caused by VZV and their impact on patients' daily lives.

I recommend to accept the paper and see no need for a revision."

We have slightly restructured the manuscript and added section titles. This will likely facilitate the reading of this dense manuscript.

Reviewer #2:

"The authors investigate the impact of zoster and pain following virus infection on patient's daily activities using international database search. The abstract and article selection process is described sufficiently. In addition to this method two models were calculated (description and causal model). As results the authors outline domains and general concepts corresponding to references identified by a simple figure (for descriptive model). The same method is used for the so-called causal model. The results obtained are not unexpected. In terms of discussion and conclusion the reviewer is missing the central threat:

1. "The line of thoughts is jumping a little bit around from one subject to another (e. g. page 9/10 row 18-34 and row 1-4 clearly is a repetition of point 'Assessment of evidence level and development of the causal model'). Therefore it should be cancelled."

As suggested, we removed the lines that were a repetition of "Assessment of evidence level and development of the causal model".

In parallel, we restructured this paragraph in order to better outline the points of discussion and to avoid repetitions with the "Methods" section.

2. "Moreover, a part of discussion is dealing with limitations (e. g. quality of life, page 10, row 5-13). In general, this explanation is correct, but the position should be placed at the beginning or at the end."

We placed the section about quality of life at the end of the "Discussion and conclusion" section, as advised.

3. "The term 'pain' is discussed on page 10 row 15-34. This thoughts are interrupted by 'unmet need' from row 8-13 and direct costs and so on. On row 15 the authors repeatedly are discussing the issue 'pain'."

We restructured this part of the manuscript in order to keep and discuss only the concepts and associations that were identified in the descriptive and causal models.

In addition, in regards to the reviewer's concern about the length of the manuscript, we removed lines throughout this part (Page 10, lines 17-29; page 11, lines 2-4, 9-12) and relocate them in the "Results" section, where they support and facilitate the reading of the figures that are proposed. Also, we have made some changes: the revised discussion is now structured so that there is a brief introduction and summary of what has been done during the work, the rationale and the main result (Page 9, lines 3-21); then the place of 'pain' and the other concepts identified in the descriptive model and the impact

represented in the causal model (Page 9, lines 23-32; page 10, lines 1-9); pain and therapeutic strategy (Page 10, lines 11-24); the instruments available (Page 10, lines 26-34); the additional research that should be done and the main limitation of the work (Page 11, lines 1-19). We hope this will help the reader to get to the critical points of the work more easily.

4. "Finally, to make a long story short: The discussion should be outlined more systemically especially in terms of separation between methodological and specialized issues. Redundancies should be eliminated. Regardless of the critical points the manuscript should be shortened substantially." As suggested, we shortened the manuscript, especially the "Discussion" section (initially, 1,500 words; currently: 1,000 words) where redundancies have been removed. We restructured the paragraphs of the discussion and relocated result parts in its respective section to better outline and highlight the critical points. We have added titles in the "Methods" and "Results" sections, which should also contribute to a higher clarity and ease of reading.

We took into consideration the points raised above and revised the manuscript accordingly to reinforce the comprehension and strength of the paper and its discussion, and to shorten it to help readers go to the point.

We hope that the revisions and answers to your questions and comments meet your expectations, and that you will consider our revised manuscript for publication. Should you need more information or have question, please do not hesitate to contact us.

Yours sincerely,

Benoit Arnould, on behalf of the co-authors

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1 **Title: The impact of herpes zoster and subsequent chronic pain on patients' daily lives**

2

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21 Category: Original Article

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1
2 **Abstract**

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5 4 Aim: The aim of our study was to carry out a literature review and develop a model
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7 5 illustrating the domains of patients' lives that are impacted by herpes zoster (HZ) and
8
9 6 subsequent chronic pain.

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12 8 Subject and Methods: Biomedical databases and online congress archives were searched
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14 9 using keywords related to HZ or post-herpetic neuralgia (PHN) and social, psychological or
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16 10 physical impact. 733 abstracts were reviewed. 29 publications containing concepts reported
17
18 11 by patients were retained for the model. Wilson and Cleary's Model was used to organise the
19
20 12 findings. Links between concepts were documented on three levels; *hypothesis, observation*
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22 13 and *evidence*. The final model illustrates the concepts impacted by HZ and PHN, relationships
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24 14 between these concepts and the level of evidence identified.

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26 15 Results: The concepts identified from the articles were grouped into the following categories:
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28 16 *Biological/Physiological, Symptom Status, Functional Status, Health Perceptions,*
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30 17 *Characteristics of the Individual, Health-Related Quality of Life (HRQOL), Treatment and*
31
32 18 *Characteristics of the Environment*. Evidence exists that HZ-related pain directly impacts
33
34 19 Functional Status, Health Perceptions and HRQOL.

35 20 Conclusion: Patients report that all major domains of life are impaired by HZ or subsequent
36
37 21 chronic pain. HZ and its painful and debilitating complications can have a substantial impact
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39 22 on physical, psychological, social and role functioning, HRQOL and activities of daily living.
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41 23 The impact on elderly patients needs to be further assessed with appropriately designed and
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43 24 validated instruments, with specific attention paid to dependence.

44 25
45 26 Keywords: Pain, Herpes Zoster, Post-herpetic Neuralgia, Quality of Life, Patient-Reported
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47 27 Outcomes, Conceptual Model
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Introduction

After primary infection with chickenpox, usually during childhood, the varicella zoster virus (VZV) becomes latent. Its reactivation causes herpes zoster (HZ), characterised by a painful vesicular rash and associated with substantial discomfort. It is often accompanied by spontaneous burning pain, parasthesias, itch and allodynia (Binder et al., 2008; Dwyer and Cunningham, 2002; Fields et al., 1998; Schmader and Dworkin, 2008). HZ is a common illness, with an estimated lifetime incidence of 20 to 30% (Brisson and Edmunds, 2003; Gauthier et al., 2008; Hope-Simpson, 1965; Schmader, 2001). Its prevalence rises with age (Chapman et al., 2003; Gauthier et al., 2008; Bowsher, 1999) ; the lifetime risk is estimated to increase to 50% in those aged > 85 years (Miller et al., 1993; Schmader, 2001).

HZ can be associated with serious complications including post-herpetic neuralgia (PHN), encephalitis, HZ ophthalmicus, facial nerve paralysis, VZV retinitis, cornea affection and glaucoma (Dworkin et al., 2007; Oxman, 2000; Schmader and Dworkin, 2008).

While PHN is the most frequent complication (Dworkin et al., 2007; Johnson, 2001; Wareham and Breuer, 2007), its true incidence remains difficult to determine due to different definitions, methodologies and study populations. PHN persisting at 3 months after rash onset may occur in 10-20% of HZ patients aged over 50 years (Gauthier et al., 2008; Johnson and Rice, 2007; Oxman et al., 2005; Scott et al., 2006). The incidence of PHN also increases with age (Bowsher, 1999; Goh and Khoo, 1997).

Patient-Reported Outcomes (PROs) can provide valuable data regarding the impact of disease as perceived by patients themselves. The term PRO refers to any health-related data collected directly from the patient (Acquadro et al., 2003). These measures are increasingly used in clinical research (Marquis et al., 2006) (Patrick et al., 2007) and are recognised as a way of reliably and validly assessing symptoms such as pain, functional limitations and health-related quality of life (HRQOL) to supplement standard clinical and physiological criteria (Schipper, 1990; Spilker, 1990; Wilson and Cleary, 1995).

The patients' perspective is recognised as particularly relevant in painful conditions (Committee for Medicinal Products for Human Use, 2007); it is acknowledged that painful chronic conditions are a major cause of impaired HRQOL (Vetter, 2007). The level of pain

1 experienced by patients with HZ or PHN can be very high (Schmader et al., 2007), and thus is
2 likely to impact patients' daily lives, especially in the elderly. As existing treatments do not
3 adequately control pain in a large proportion of patients (Wu and Raja, 2008; Rowbotham and
4 Petersen, 2001) the assessment of disease burden is particularly interesting in this population.
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9 The aim of this study was to systematically review the published research on the impact of
10 HZ and PHN, from the patients' perspective. The specific objectives of the work were to: 1)
11 list all domains of patients' lives reported as impaired by HZ and PHN, 2) identify the
12 hypothesised relationships between these domains; 3) assess the level of published evidence
13 supporting the causality of HZ and PHN in these impairments.
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1 **Methods**

3 **Systematic literature review**

4 Information sources

5 The search was conducted in March 2007, exploring MEDLINE, EMBASE and PsycINFO,
6 and the Mapi Research Trust's database of publications on PROs (<http://www.mapi-trust.org/>); International Society for Pharmacoeconomics and Outcomes Research (ISPOR)
7 and International Society for Quality of Life Research (ISOQOL) abstracts from 2004 to
8 2006.

10 Search strategy

11 Search criteria were defined as follows: articles written in English and including an abstract,
12 published since 1980 and reporting on the adult population. The searches were carried out
13 using a combination of the following Medical Subject Headings (MeSH): *herpes zoster, post-*
14 *herpetic neuralgia, quality of life, psychological adaptation, pain measurement, activities of*
15 *daily living, patient satisfaction, health status and cost of illness*, and the following non-
16 MeSH keywords: *functioning, conceptual framework, and impact social, dependence,*
17 *symptoms and instrumental activities of daily living.*

18 Abstract selection

19 Selection and rejection criteria were determined as follows: abstracts were retained if they
20 mentioned either PRO concepts related to the impact of HZ, PHN or neuropathic pain on
21 patients' lives, or questionnaires measuring patients' perspectives on these impacts. Abstracts
22 reporting environmental or patient characteristics related to the occurrence, frequency or
23 severity of HZ or PHN were also retained. Abstracts were rejected if they were not specific to
24 HZ, PHN or neuropathic pain, if only clinical pain was described, or if the study presented did
25 not mention PRO concepts or questionnaires. Seven hundred and thirty-three abstracts were
26 retrieved and reviewed by two researchers independently. Abstracts were selected when an
27 agreement between them was reached. Six hundred and thirty-six abstracts did not meet the
28 selection criteria, or met one of the rejection criteria and were rejected.

29 Article selection

30 Ninety-seven articles were ordered and reviewed in detail. Sixty-eight articles were rejected
31 for one of the following reasons: the target population was not clearly defined, concepts
32 impacted by HZ or PHN were not mentioned, or the studies did not include instruments
33 measuring the impact of HZ or PHN on patients.

1 Twenty-nine articles were selected for inclusion in the models. Relevant data from the final
2 set of articles selected was recorded in specific extraction tables. From each article, detailed
3 information was retained on the aim of the study, the population, the country, the
4 questionnaires used and the PRO concepts.

6 **Development of the models**

7 The information extracted from the selected articles was used to develop two models about
8 the impact of HZ and PHN on patients' lives: a first one providing an organised summary of
9 all concepts identified – this is the descriptive model – and a second one showing only
10 published evidence on causal relationships between these concepts – this is the causal model.

12 Selection of concepts and development of the descriptive model

13 The data extracted from the articles was used to develop a comprehensive model illustrating
14 the impact of HZ and PHN on patients' lives. Wilson and Cleary's model (Wilson and Cleary,
15 1995) was taken as a basis for the structure of our models. The model developed by Wilson
16 and Cleary contains 5 central domains that are likely to be impacted by a disease or disorder:
17 Biological and Physiological Variables, Symptom Status, Functional Status, General Health
18 Perceptions and Overall Quality of Life. In addition to these, factors which can influence the
19 impact of disease on patients' lives are grouped in two other general domains: Characteristics
20 of the Individual, and Characteristics of the Environment. All of the PRO concepts identified
21 in the selected articles were organised according to these domains to develop a specific
22 descriptive model of HZ and PHN. One specific new domain – Treatment - was added in
23 order to complete the picture.

24 Assessment of evidence level and development of the causal model

25 The causal relationship between the concepts was then studied at three levels of evidence:
26 *tested hypothesis*, *observed information*, or *hypothesis*. Causal relationships supported by
27 positive statistical testing of predefined hypotheses that were listed among the study
28 objectives were categorised as *tested hypothesis*; other causal relationships supported by the
29 study data (correlations or tests) were categorised as *observed information*; and causal
30 relationships mentioned in the introduction or discussion of the article, but not supported by
31 the study data, were categorised as *hypotheses*. The causal model that was then developed to
32 illustrate the relationships includes only the domains and concepts for which the highest level
33 of evidence (*tested hypothesis*) was identified in the form of results from a population-based
34 study.

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2 **Results**

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5 4 The PRO questionnaires that were referenced in the publications included in the review can
6 be found in Table 1. The questionnaires are listed according to the domains measured which
7 are: Characteristics of the Individual, Symptom Status, Functional Status, Health Perceptions,
8 Characteristics of the Environment, and QOL. The publications in which these questionnaires
9 were cited or used are referenced in the table.

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15 - Here Table 1 -
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18 **Descriptive model**

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20 12 The model details the concepts identified from the literature search, irrespective of the level of
21 evidence provided by the authors. It is organised into 8 distinct domains: Characteristics of
22 the Individual, Biological/Physical, Symptoms Status, Functional Status, Health Perceptions,
23 Characteristics of the Environment, HRQOL and Treatment. Each domain contains a number
24 of general concepts identified in the referenced articles. Figure 1 is the descriptive model of
25 all of these domains and general concepts. Symptoms associated with HZ and PHN comprised
26 pain, rash, cutaneous manifestations, fever and discomfort. Beyond these symptoms, HZ and
27 PHN had negative effects on physical functioning, activities of daily living, psychological and
28 social functioning, including well-being (van Seventer et al., 2006), depression (Katz et al.,
29 2004), social isolation and withdrawal (Mauskopf et al., 1994; Schmader, 1999).

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42 **Causal model**

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44 25 When the relationship between the different domains was studied in detail, the domains found
45 to be directly impacted by HZ pain and PHN were: Functional Status (Katz et al., 2004;
46 Lydick et al., 1995; Mauskopf et al., 1994; van Seventer et al., 2006), Health Perceptions (van
47 Seventer et al., 2006) and HRQOL (Chidiac et al., 2001; Katz et al., 2004; Lydick et al., 1995;
48 Mauskopf et al., 1994; Schmader, 1999; van Seventer et al., 2006). Figure 2 is the model
49 illustrating these relationships. Functional Status contains basic functions such as sleep and
50 physical mobility, directly impacted by HZ pain and PHN. It also includes Physical Function,
51 which is affected to the extent of interfering with activities of daily living. Health Perceptions
52 is affected in terms of the Health Status of patients. HRQOL comprises complex concepts
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1 such as depression and psychological impairment, as well as serious social impacts such as
2 social withdrawal and isolation. The functional and social impacts of this pain pose a longer-
3 term threat to patients, and can lead to limitations and handicap, especially in the elderly
4 (Schmader, 1999). In old age, patients become vulnerable to acute diseases and harmful
5 events, which are likely to trigger a shift to dependence.

6 Other clinical factors such as fatigue and depression in addition to pain are reported to impact
7 patients' lives, such as crusting and healing (Mauskopf et al., 1994). However, the level of
8 available evidence regarding how far these have specific detrimental effects is not as strong as
9 it is for pain.

10 Direct costs for medical treatment of HZ and PHN are high and the functional, psychological,
11 social and further medical difficulties that can be caused by an episode of PHN are costly as
12 well (Johnson, 2004). PHN also causes loss of work time (Scott et al., 2006).

13 - Here Figure 2 -
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1 Discussion and Conclusions

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4 3 With the rapid expansion of the elderly population in Western countries (Giannakouris, 2008),
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6 4 the prevalence of HZ is expected to continue to rise, and public health policies must be
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8 5 adapted to the actual severity of these conditions.
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11 7 A literature review is not experimental research. During the process of accessing sources,
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13 8 selecting articles, extracting the useful information, and organising it, various biases are likely
14
15 9 to occur. In order to optimise the reliability and reproducibility of our findings, we applied a
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17 10 systematic approach at each stage of our work: selection of sources, extraction of data, and
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19 11 analysis. A comprehensive descriptive model and a causal model were developed from the
20
21 12 systematic literature review. The level of available evidence in causal model relationships was
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23 13 assessed according to predefined rules that enabled the relationships between the concepts to
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25 14 be categorised as *tested hypothesis*, *observed information* or *hypotheses*. The first model
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27 15 highlighted the impact of HZ and PHN symptoms on all aspects of the patients' lives. As
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29 16 such, it fits remarkably well with the generic model developed by Wilson and Cleary that
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31 17 describes the relationships between clinical parameters and HRQOL (Wilson and Cleary,
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33 18 1995). HZ pain and PHN were identified as the trigger of every causal relationship, and the
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35 19 only element of the Symptoms Status domain for which sufficient evidence was identified.
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37 20 The causal model gave evidence of relationships between symptoms status, functional status,
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39 21 health perceptions and HRQOL.
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42 23 Although HZ and PHN have been less studied from the patients' perspective than other
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44 24 common painful conditions, the scientific literature shows consensus on the impact these
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46 25 conditions have on patients' lives. The critical role of pain in HZ and PHN is consistent with
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48 26 findings in various other painful diseases and conditions, where pain has been identified as
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50 27 the primary cause of negative effects on several functions (Neumann et al., 2000; Wolfe and
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52 28 Hawley, 1997). With pain episodes that are frequently reported by these patients to be
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54 29 particularly severe, pain is considered the major driver of impairment in functioning, health
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56 30 perceptions, and HRQOL. The descriptive and causal models suggest that the combination of
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58 31 impaired physical, psychological, and social functioning resulting from HZ and PHN is likely
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60 32 to have irreversible consequences on patients' lives after a certain age. However, to our
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1 knowledge, no epidemiological data are available on the impact of HZ or PHN episodes on
2 institutionalisation rates or other indicators or measures of dependence.

3 As regards the other non-painful symptoms, even if they have been reported to impact
4 patients' lives, further research needs to be conducted to confirm these assumptions and
5 assess the magnitude of the specific impact non-painful symptoms have on patients' lives.

6 Economic and epidemiologic data confirm the importance of unmet needs in the current
7 management of HZ and PHN (Johnson et al., 2007). Moreover the economic consequences of
8 these conditions are exacerbated as an episode of PHN can be lengthy: after 1 year, 5%-10%
9 of patients still experience pain (Johnson, 1995).

10
11 Pain being a lasting symptom in particular of PHN, it is one of the main targets of
12 pharmacologic treatment (Johnson et al., 2008). However, the specific vulnerability of the
13 elderly, for whom temporary dysfunction easily turn into permanent disability, highlights the
14 need for strategies centred not on this specific symptom but on the patient. Recent
15 recommendations for HZ management include broader non-pharmacologic approaches such
16 as social support and patient education (Schmader and Dworkin, 2008) (Wu and Raja, 2008),
17 especially for the elderly (Dworkin et al., 2007). An alternative to therapeutic strategy is
18 prevention and early treatment of HZ in order to lower the incidence of PHN. The prevention
19 of HZ is expected to reduce the costs associated with HZ and PHN (Cunningham et al., 2008).
20 A HZ vaccine has proven effective in reducing incidence and severity of HZ and PHN,
21 especially in individuals aged > 60 (Oxman and Levin, 2008). Vaccination was also
22 associated with improvements in key patient-reported domains such as a reduced interference
23 with activities of daily living (Gnann, Jr., 2008). Further long-term population-based studies
24 are expected in order to examine the epidemiological impact of these vaccination
25 programmes.

26
27 A number of generic and specific PRO questionnaires have been developed, validated and
28 used in clinical research to provide a means of assessing the patient's perspective in various
29 diseases and conditions (Chassany et al., 2002). Only a few specific measures have been
30 developed to assess the impact of HZ and PHN as perceived by the patients, including the
31 Zoster Brief Pain Inventory (Coplan et al., 2004) and the Zoster Impact Questionnaire
32 (Schmader et al., 2007). However, studies identified in the present analysis often used
33 questionnaires that are not specific to the population or to the disease area being considered.

1 Specific measurement instruments need to be developed and validated for an adequate,
2 reliable and sensitive assessment of these changes, especially in elderly people.

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5 4 Additional research is needed to complete and consolidate the picture of the detrimental effect
6 of HZ and PHN on patients' lives: first, prospective longitudinal studies are needed to provide
7 5 estimates of the impact of painful episodes and to quantify how much this impact can be
8 6 limited with new strategies, such as prevention; and then, the assumption regarding the impact
9 7 of HZ and PHN on the level of dependence – an assumption which is strongly supported by
10 8 the impact models based on published data - needs specific epidemiology studies to be
11 9 conducted for confirmation and quantification.

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20 12 One limitation that could be raised for this literature review is the approximate labelling, or
21 13 naming of concepts, and lack of appropriate definitions are a source of confusion that
22 14 frequently surrounds a number of concepts that are dealt with in the literature; the most
23 15 common confusion lies in the misuse of the term Quality of Life as an umbrella term for
24 16 patient-related symptoms, function, HRQOL, and health status, whereas Quality of Life is a
25 17 specific notion with recognised definitions (Schipper, 1990; Spilker, 1990). Despite our
26 18 awareness of the risk of confusion in the terms used, the models proposed in the present
27 19 article provide an organisation of the PRO concepts based on the original terminology used by
28 20 the authors of the selected publications, even when the concepts were not explicitly defined or
29 21 illustrated with items showing face validity.

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5 4 the manuscript, and Claire Marant for performing the literature search.
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11 7 **Conflict of interest**

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1 **Legends for Figures**

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3 Figure 1. Descriptive model: domains, general concepts and their references identified in
4 relation to HZ and PHN. The figure is based on Wilson and Cleary’s model, but does not
5 illustrate causal relationships.

6

7 Figure 2. Causal model: the patient-reported impact of HZ pain and PHN. Arrows indicate
8 direction of causal relationship.

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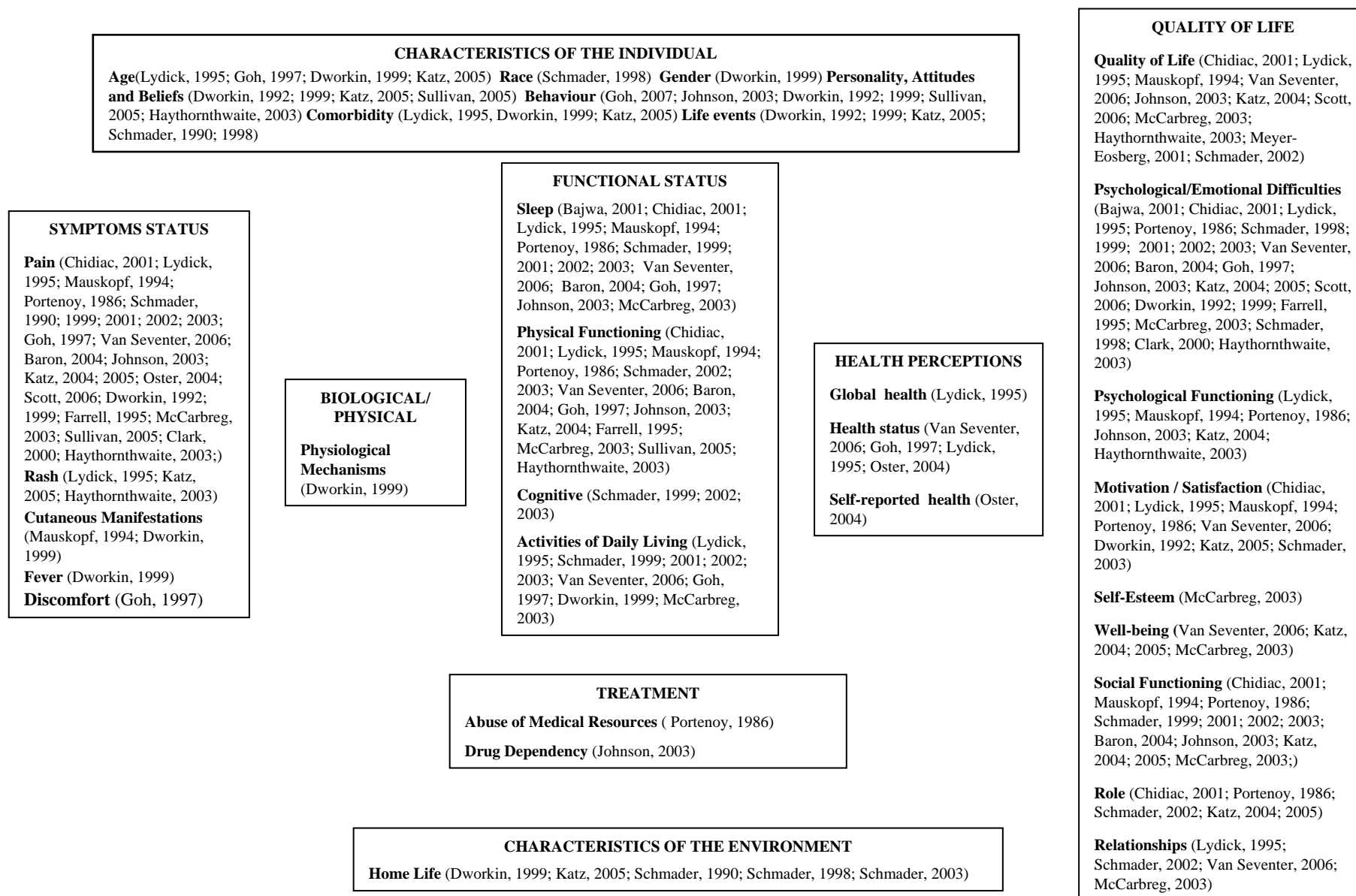
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Table 1. PRO questionnaires identified in literature review

Domain	Instrument
Characteristics of the Individual	Charlson Comorbidity Index - Lydick E, 1995 Coping Strategies Questionnaire (CSQ) -Haythornthwaite JA, 2003 Dysfunctional Attitude Scale (DAS) - Dworkin RH, 1992 Illness Behaviour Questionnaire (IBQ) - Dworkin RH, 1992 ; Katz J, 2005 Multidimensional Health Locus of control (MHLC) - Katz J, 2005 National Institute of Mental Health Diagnostic Interview Schedule (NIMH DIS) -Clark MR, 2000 Pain Catastrophizing Scale (PCS) - Sullivan MJL, 2005 Personality Disorder Questionnaire (PDQ) - Katz J, 2004 ; Katz J, 2005 Spielberger State Trait Anxiety Inventory (STA) - Dworkin RH, 1992; Katz J, 2004 ; Katz J, 2005 Somatic Symptom Index - Katz J, 2005 Somatosensory Amplification Scale - Katz J, 2005
Symptoms Status	Wisconsin Brief Pain Inventory (BPI) - Lydick E, 1995 Modified Short Form Brief Pain Inventory (mBPI-SF) - Van Seventer R, 2006 Gracely scales - Mauskopf J, 1994 Items on PHN pain intensity - Oster G, 2004 MOS Pain Index - Katz J, 2004 ; Katz J, 2005 Mc Gill Pain Questionnaire (MPQ) - Dworkin RH, 1992 ; Katz J, 2004 Short-form Mc Gill Pain Questionnaire (MPQ-SF) - Farrell MJ, 1995 ; Sullivan MJL, 2005 Numerical Rating Scale for Pain - Haythornthwaite, 2003 West Haven-Yale Multidimensional Pain Inventory (WHYMP) - Haythornthwaite JA, 2003 Zoster Brief Pain Inventory (ZBPI) - Available in appendix of Coplan PM, 2004 ; Scott FT, 2006
Functional Status	6-point scale measuring the effect of pain on patients' ability to perform ADL - Mauskopf J, 1994 Human Activity Profile (HAP) - Farrell MJ, 1995 Pain Disability Index (PDI) - Sullivan MJL, 2005 Zoster Brief Pain Inventory (ZBPI) - Coplan PM, 2004 ; Scott FT, 2006
Health Perceptions	100-point global health rating scale - Oster G, 2004 Self-reported overall health rating, and health resource utilisation - Van Seventer, 2006
Characteristics of the Environment	Geriatric Scale of Recent Life Events (GSRLE) - Schmader K, 1990 ;Schmader K, 1998 Life Stressors and Social Resources Inventory (LSSRI) - Katz J, 2005 Schedule of Recent Experience (SRE) - Dworkin RH, 1992
Quality of Life	Beck Depression Inventory (BDI) - Dworkin RH, 1992 ; Katz J, 2004 ; Katz J, 2005 Geriatric Depression Scale (GDS) - Farrell MJ, 1995 EQ-5D - Oster G, 2004 ; Scott FT, 2006 ; Van Seventer R, 2006 Hospital Anxiety and Depression (HAD) - Scott FT, 2006 Life Satisfaction in the Elderly Scale (LSES) - Dworkin RH, 1992 Mental Health Inventory (MHI) - Katz J, 2004 ; Katz J, 2005 Nottingham Health Profile (part 1) (NHP) - Mauskopf J, 1994 ; Meyer-Eosberg K, 2001 Hopkins symptom checklist 90-R(SCL-90-R) - Clark MR, 2000 SF-36 - Chidiac C, 2001 ; Katz J, 2004 ; Katz J, 2005 ; Lydick E, 1995 ; Meyer-Eosberg K, 2001 Social Interaction Scale (SIS) - Schmader K, 1998 Social Network Scale (SNS) - Schmader K, 1998

Figure 1.



CHARACTERISTICS OF THE INDIVIDUAL

Age(Lydick, 1995; Goh, 1997; Dworkin, 1999; Katz, 2005) **Race** (Schmader, 1998) **Gender** (Dworkin, 1999) **Personality, Attitudes and Beliefs** (Dworkin, 1992; 1999; Katz, 2005; Sullivan, 2005) **Behaviour** (Goh, 2007; Johnson, 2003; Dworkin, 1992; 1999; Sullivan, 2005; Haythornthwaite, 2003) **Comorbidity** (Lydick, 1995, Dworkin, 1999; Katz, 2005) **Life events** (Dworkin, 1992; 1999; Katz, 2005; Schmader, 1990; 1998)

QUALITY OF LIFE

Quality of Life (Chidiac, 2001; Lydick, 1995; Mausekopf, 1994; Van Seventer, 2006; Johnson, 2003; Katz, 2004; Scott, 2006; McCarbreg, 2003; Haythornthwaite, 2003; Meyer-Eosberg, 2001; Schmader, 2002)

Psychological/Emotional Difficulties (Bajwa, 2001; Chidiac, 2001; Lydick, 1995; Portenoy, 1986; Schmader, 1998; 1999; 2001; 2002; 2003; Van Seventer, 2006; Baron, 2004; Goh, 1997; Johnson, 2003; Katz, 2004; 2005; Scott, 2006; Dworkin, 1992; 1999; Farrell, 1995; McCarbreg, 2003; Schmader, 1998; Clark, 2000; Haythornthwaite, 2003)

Psychological Functioning (Lydick, 1995; Mausekopf, 1994; Portenoy, 1986; Johnson, 2003; Katz, 2004; Haythornthwaite, 2003)

Motivation / Satisfaction (Chidiac, 2001; Lydick, 1995; Mausekopf, 1994; Portenoy, 1986; Van Seventer, 2006; Dworkin, 1992; Katz, 2005; Schmader, 2003)

Self-Esteem (McCarbreg, 2003)

Well-being (Van Seventer, 2006; Katz, 2004; 2005; McCarbreg, 2003)

Social Functioning (Chidiac, 2001; Mausekopf, 1994; Portenoy, 1986; Schmader, 1999; 2001; 2002; 2003; Baron, 2004; Johnson, 2003; Katz, 2004; 2005; McCarbreg, 2003;)

Role (Chidiac, 2001; Portenoy, 1986; Schmader, 2002; Katz, 2004; 2005)

Relationships (Lydick, 1995; Schmader, 2002; Van Seventer, 2006; McCarbreg, 2003)

FUNCTIONAL STATUS

Sleep (Bajwa, 2001; Chidiac, 2001; Lydick, 1995; Mausekopf, 1994; Portenoy, 1986; Schmader, 1999; 2001; 2002; 2003; Van Seventer, 2006; Baron, 2004; Goh, 1997; Johnson, 2003; McCarbreg, 2003)

Physical Functioning (Chidiac, 2001; Lydick, 1995; Mausekopf, 1994; Portenoy, 1986; Schmader, 2002; 2003; Van Seventer, 2006; Baron, 2004; Goh, 1997; Johnson, 2003; Katz, 2004; Farrell, 1995; McCarbreg, 2003; Sullivan, 2005; Haythornthwaite, 2003)

Cognitive (Schmader, 1999; 2002; 2003)

Activities of Daily Living (Lydick, 1995; Schmader, 1999; 2001; 2002; 2003; Van Seventer, 2006; Goh, 1997; Dworkin, 1999; McCarbreg, 2003)

HEALTH PERCEPTIONS

Global health (Lydick, 1995)

Health status (Van Seventer, 2006; Goh, 1997; Lydick, 1995; Oster, 2004)

Self-reported health (Oster, 2004)

SYMPTOMS STATUS

Pain (Chidiac, 2001; Lydick, 1995; Mausekopf, 1994; Portenoy, 1986; Schmader, 1990; 1999; 2001; 2002; 2003; Goh, 1997; Van Seventer, 2006; Baron, 2004; Johnson, 2003; Katz, 2004; 2005; Oster, 2004; Scott, 2006; Dworkin, 1992; 1999; Farrell, 1995; McCarbreg, 2003; Sullivan, 2005; Clark, 2000; Haythornthwaite, 2003;)

Rash (Lydick, 1995; Katz, 2005; Haythornthwaite, 2003)

Cutaneous Manifestations (Mausekopf, 1994; Dworkin, 1999)

Fever (Dworkin, 1999)

Discomfort (Goh, 1997)

BIOLOGICAL/ PHYSICAL

Physiological Mechanisms (Dworkin, 1999)

TREATMENT

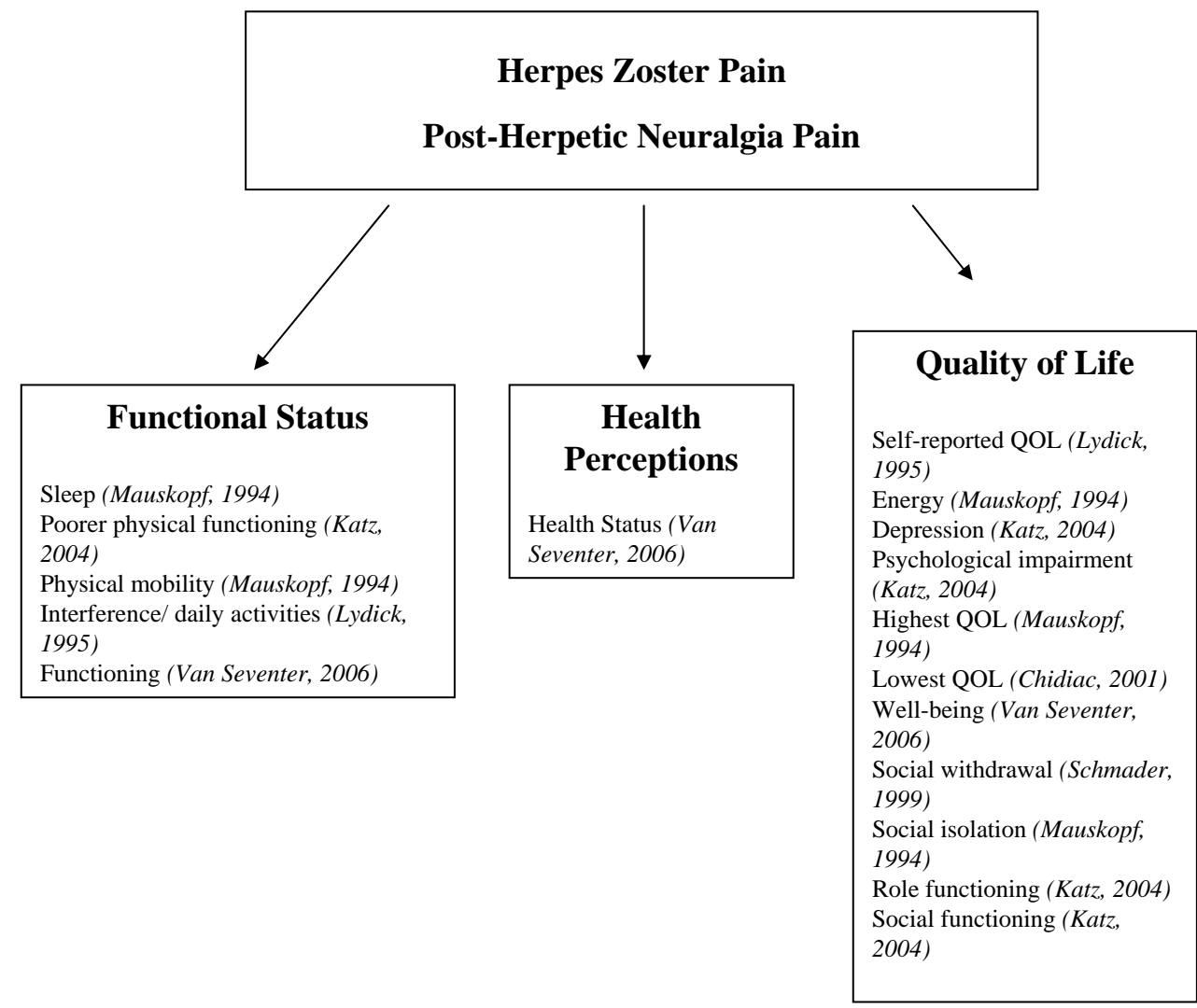
Abuse of Medical Resources (Portenoy, 1986)

Drug Dependency (Johnson, 2003)

CHARACTERISTICS OF THE ENVIRONMENT

Home Life (Dworkin, 1999; Katz, 2005; Schmader, 1990; Schmader, 1998; Schmader, 2003)

Figure 2.



Supplementary Material

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