Blood test ordering for unexplained complaints in general practice. Results of the VAMPIRE study on diagnosis and prognosis
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Citation for published version (APA):

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Chapter 1

General introduction
General introduction

The topic of this thesis is the diagnosis and prognosis of patients presenting with unexplained complaints in general practice, while paying special attention to the role of blood test ordering. In this general introduction, the topic is elaborated upon by a discussion of the definition, course, epidemiology and various aspects of blood test ordering for patients with unexplained complaints in general practice. Finally, the research questions, methods and outline of thesis are introduced.

From experiencing health complaints to presenting unexplained complaints in health care

Many people experience health complaints in daily life. In a Dutch study for example, 89% of the population reported to have experienced one or more health complaints over the last two weeks\(^1\). These health complaints most often are not sufficient reason to visit a physician. In the Netherlands, general practitioners (GPs) are the first in line to provide medical care, and each patient is registered with his or her own GP. Patients experiencing complaints for which they do wish to see a doctor, will start by visiting their GP. If after adequate history taking and physical examination the GP is unable to establish a specific diagnosis, the complaints are defined ‘unexplained complaints’ according to the Dutch College of General Practitioners (DCGP) in their guideline on blood test ordering\(^2\). Fatigue, abdominal complaints and musculoskeletal complaints are recurring examples of unexplained complaints\(^3,4\).

From newly presented unexplained complaints in health care to established unexplained complaints

Over the course of time, these newly presented unexplained complaints may turn out to be the symptoms of various diagnoses. First of all, they may turn out to be self-limiting complaints (in 90% of cases within one month\(^5,6\)). They may also represent the first signs of a distinct explained disease (rough estimate: in less than 5% of cases\(^7\)). Finally, they may turn out to remain unexplained after follow-up (established unexplained complaints). In international literature, established unexplained complaints are often referred to as medically unexplained symptoms (MUS). Established unexplained complaints are sometimes interpreted as functional symptoms/syndromes (e.g. irritable bowel syndrome, chronic fatigue syndrome) or as signs of undifferentiated somatoform disorders. Though all types of established unexplained complaints mentioned above (MUS, functional symptom/syndrome diagnoses or undifferentiated somatoform disorders) are related to the type of complaints focused on in this
thesis, they all imply to be a ‘diagnosis after follow-up’, or, in some cases, a
‘diagnosis by exclusion’. Those established unexplained complaints were at one
time sufficient reason for a patient to consult their GP. This thesis focuses on
patients presenting with unexplained complaints.

Epidemiology

Unexplained complaints account for 3-39% of the consultations in general
practice. This wide variation in prevalence depends on the applied definition of
unexplained complaints, the moment in the complaint episode at which the
diagnosis is established, and on inter-doctor variation. Melville et al. found that 3% of the patients with a new illness episode had MUS
after three months. In the UK study of Peveler et al., for example, GPs
identified MUS as the main reason for encounter for 19% of the attending
patients. Screening instruments identified 35% of these patients as having
multiple MUS, 5% of whom were probable cases of somatoform disorders. In a
Dutch study, Van der Weijden et al. found that on average 13% of the
consultations involved at least one complaint considered unexplained by GPs.
The highest prevalence was found by Plowsky, who found that 39% of planned
consultations in Australian primary care concerned patients presenting
unexplained complaints. The prevalence of unexplained complaints after first consultations will obviously
differ from the prevalence of established unexplained complaints.

A large inter-doctor variation in labelling presented health complaints as
unexplained is another cause of the variety in the prevalence of unexplained
complaints. A complaint considered ‘unexplained’ by the first GP, may be
perfectly explainable to the next. Some GPs may need pathological or
anatomical substrates to label a complaint ‘explained’, while for others
functional symptoms or syndromes suffice to explain the health complaints
experienced by patients, and they do not require such substrates.

Blood test ordering

Because unexplained complaints may in time turn out to be the symptoms of
various diseases, GPs will always experience a certain level of diagnostic
uncertainty. Therefore, in the work-up of patients who present new unexplained
complaints, diagnostic tests are frequently added to history taking and the
physical examination. Some authors even recommend ordering laboratory
tests. However, there are various arguments why GPs should be cautious in
ordering additional blood tests for patients presenting unexplained complaints
for the first time. Because of the low prior risk of serious somatic disease in
these patients, the risk of false positive test results is relatively high. False
positive test results may in turn lead to a cascade of unnecessary additional test
ordering, referrals and treatments, as well as to anxiety and even somatisation\textsuperscript{14,15}. Therefore, in its guideline on blood test ordering, the DCGP advises GPs to postpone blood test ordering for patients presenting with unexplained complaints for the first time for four weeks. If blood tests are ordered, GPs are advised to restrict the test orders to haemoglobin (Hb), erythrocyte sedimentation rate (ESR), glucose and thyroid stimulating hormone (TSH)\textsuperscript{2}. The choice of these tests is partly prevalence driven: anaemia, inflammation/infection, diabetes and hypothyroidism are diseases that may start off with unexplained complaints and are quite prevalent in general practice. However, the guideline is consensus-based with respect to both the postponement advice and the selection of blood tests. It is unknown what the accuracy of immediate or postponed blood test ordering is for patients who present with unexplained complaints in general practice, nor which or how many blood tests should be ordered.

Postponement of blood test ordering

Physicians do not always postpone blood test ordering for patients with unexplained complaints\textsuperscript{3}. They mention strategic reasons or say they order blood tests to exclude a disease, because the predictive value of a negative test result is high, while the risk of serious somatic disease is low. However, the pre-test probability of negative test results is already very high among patients with unexplained complaints, so the additional diagnostic yield of blood test ordering is probably marginal. Furthermore, GPs feel the need for blood test ordering in order to reassure patients that there is nothing to be anxious about. According to them, blood test ordering is expected by their patients, and what they need to do to keep them satisfied. However, the evidence for the effectiveness of this reassurance by blood test ordering and for patients’ expectations concerning blood test ordering is lacking. Postponing blood test ordering can be regarded as using time as a diagnostic tool. When using the tincture of time by postponing blood test ordering, the number of patients to be tested will diminish. The hypothesis is that for patients who still have complaints after one month and who decide to revisit their GP, the prior probability for a somatic disease has increased. As a result, fewer false-positive test results are to be expected if blood test ordering is postponed for patients who present with unexplained complaints in general practice. Of course, the decision to test immediately or to postpone blood test ordering is a complex one, influenced by factors such as diagnostic uncertainty, therapeutic options, prognostic considerations, the doctor-patient relationship, and policy and organization-related factors\textsuperscript{16}. 
Research on established unexplained complaints

Most research in the field of unexplained complaints focuses on established unexplained complaints, the situation after follow-up or after exclusion of any disease. This research ranges from discussions on nomenclature and taxonomy\textsuperscript{17-19}, to research on the characterization of these patient groups\textsuperscript{20,21} and possible treatment options such as anti-depressants and cognitive behaviour therapy\textsuperscript{22}.

Patients with established unexplained conditions tend to consume excessive medication and other health care facilities, both in primary care and specialised health care settings. Over time these patients may go through numerous hospitalizations, surgical procedures and futile treatments with the impending risk of being exposed to iatrogenic harm\textsuperscript{15,23}. Feder et al. showed that patients with established unexplained complaints were older, more often female and less likely to be married or living with a partner. They also showed more psychiatric co-morbidity and an impaired quality of life\textsuperscript{20}. GPs often regard these patients as ‘heart sink patients’, with whom they feel impotent in the sense of an angry helplessness\textsuperscript{24}. These established unexplained complaints may also affect the relationship between physician and patient. Physicians may become frustrated or annoyed with patients they cannot understand or help. Furthermore, patients often feel that they are not taken seriously or helped out, and feel that they are treated as malingerers. They therefore tend to lose faith in their GPs\textsuperscript{25}. It can be concluded that the consequences of ongoing, established unexplained complaints are unfavourable.

Vague Medical Problems In REsearch (VAMPIRE) study

In brief, research has been performed predominantly in the field of established unexplained complaints. There are, however, many unresolved issues concerning patients presenting with unexplained complaints in general practice. The value of (postponed) blood test ordering and the course of these newly presented unexplained complaints over time and its determinants in particular need clarification. We have developed the VAMPIRE trial to shed some light on these issues.
Research questions

The research questions of the study were:
1. What are the characteristics (in terms of demographics and quality of life) of patients presenting with unexplained complaints in general practice?
2. How many and which blood tests are ordered by GPs for patients with unexplained complaints in general practice?
3. What are patient and consultation-related determinants of GPs’ decisions to order blood tests immediately for patients presenting with unexplained complaints in general practice?
4. What is the yield of blood test ordering for patients presenting with unexplained complaints in general practice in terms of established diagnoses/evaluations after a 12-months’ follow-up and the occurrence of abnormal test results among patients with these complaints, both when tests are ordered immediately and when they are postponed?
5. What is the effect of a 4-week postponement of blood test ordering on patients’ anxiety and satisfaction as compared to an immediate test ordering strategy?
6. What is the course of unexplained complaints in terms of presence of complaints over time and complaint-related diagnoses?
7. What are the determinants of patients at risk of developing persistent (established unexplained) complaints; and what are the determinants of the course of the quality of life experienced by patients presenting with unexplained complaints?

Methods

The VAMPIRE trial was a cluster-randomised trial in which general practitioners were randomised over three groups. GPs from group 1 were instructed to order blood tests immediately and GPs from groups 2 and 3 were told to postpone blood test ordering for patients presenting with unexplained complaints. In addition, group 3 was supported in postponing blood test ordering by a systematically developed quality improvement strategy. The inclusion of patients into this study took place from February 2002 until December 2003, and concerned patients with unexplained fatigue, abdominal complaints, musculoskeletal complaints, weight changes and itch. Unexplained complaints were defined as those complaints for which the GP, after adequate history taking and physical examination could not establish a specific diagnosis. The patient follow-up ended 12 months after the initial consultation. The study was a joint venture between the Departments of General Practice of the Academic Medical Center – University of Amsterdam and Maastricht University, both in
the Netherlands. The systematic development and evaluation of a strategy to improve the blood test ordering behaviour of GPs by the application of a watchful waiting approach is discussed in another thesis\textsuperscript{26}.

Outline of thesis

The design of the VAMPIRE trial has been challenging, among other reasons due to the nature of unexplained complaints. We had to come up with a variety of solutions, not always straightforward, for the methodological barriers we encountered. These challenges and solutions are discussed in chapter 2. In chapter 3 of this thesis, the methodology of the VAMPIRE trial is presented elaborately.

After designing the trial, but before its actual start, we investigated potential patient and consultation-related determinants of GPs' decisions to order blood tests and examined the number and type of tests ordered by GPs for patients with unexplained complaints. The results are in discussed in chapter 4. Chapter 5 presents and compares the demographic characteristics and quality of life of the participants of the VAMPIRE trial at presentation.

Chapter 6 deals with the yield of blood test ordering for patients with unexplained complaints in terms of the relationship between established diagnoses and the occurrence of abnormal test results for patients with these complaints, both when tests were ordered immediately at presentation, and when they were postponed. In this chapter, we also explored whether there are consultation-related determinants that can predict the presence of abnormal blood test results.

The next chapter is chapter 7, in which the relationship between on the one hand the satisfaction and anxiety of patients with unexplained complaints, and on the other hand the two diagnostic test ordering approaches (immediate or postponed blood test ordering) is presented.

The course of unexplained complaints over time - in terms of the presence of complaints over time, established diagnoses, and quality of life and determinants of their course - is discussed in chapter 8.

As an example of the steps that are taken in evaluating new blood tests before their use in daily practice, in chapter 9, the diagnostic accuracy of carbohydrate deficient transferrin (CDT) was systematically reviewed. Excessive alcohol consumption can be one of the (hidden) causes of unexplained complaints. This relatively new blood test was supposed to have better properties for detecting excessive alcohol consumption than, for example, mean corpuscular volume (MCV) and gamma glutamyl transferase (GGT).

Finally, chapter 10 presents the general discussion, tying all previous chapters together and describing the implications for everyday GP practice and future research.
References


