PATIENT EXPERIENCES OF ADVERSE DRUG REACTIONS

By

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Abstract

Patient experience of serious ADRs and their impact on patients' lives have not been previously explored. This thesis aims to explore the experiences of patients diagnosed with drug-induced Stevens-Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN). In addition, the very elderly are a group particularly vulnerable to ADRs, and in particular, those due to antihypertensives. This thesis thus also explores the impact of such ADRs in the elderly, on managing their hypertension optimally.

Firstly, I undertook a retrospective qualitative study of adult survivors of SJS and TEN, to explore their experiences, views and perceptions. The ADR continued to affect patients' lives long after the event. Their interpretations regarding why the ADR occurred differed and may have influenced their trust in healthcare professionals and in medicines. Clear communication, and patient education and support after the event, may therefore be important.

Secondly, I undertook an analysis of internet-based personal descriptions of SJS and TEN. Authors wished to share experiences and seek advice from others, and had common concerns regarding the ADR. These findings could be used to improve the management of such patients.

Finally, I undertook a retrospective cohort study in very elderly patients to determine whether ADRs to antihypertensive drugs limit the clinician's ability to achieve blood pressure targets. Almost half the patients studied had documented ADRs which limited further intervention. Aggressive treatment of hypertension in the very elderly may therefore be difficult to achieve in practice.

Dedication

To my husband Aysam, for his unfailing support throughout the writing of this thesis, and to my family, for their constant encouragement during my research.

Acknowledgements and Declarations

Chapter 1– The introduction to this thesis is my own work. I am grateful to my supervisors, Professor Robin Ferner and Dr Una Martin, for their useful advice and discussion.

Chapter 2– The study presented in this chapter was conceived by myself, and undertaken with Dr. Anthony Cox (ARC) and Professor Robin Ferner (REF), and with whom I also published a paper based on this chapter. I am indebted to them both for their advice and support during this study. I am grateful to Dr Helen Lewis (HL) and Dr Ratna Raja, from the Department of Dermatology at Selly Oak Hospital, Birmingham, who kindly provided me with access to their database of SJS and TEN survivors. I am also grateful to Dr. Jan Oyebode and Dr Michael Larkin from the Department of Psychology at the University of Birmingham, for their comments on the qualitative analysis undertaken in the paper, and to Dr. Jonathan Ives, Research Fellow at the Centre for the study of Global Ethics at the University of Birmingham, for reviewing the research protocol and ethical aspects of the study. Finally, I would like to thank Dr Andrew Herxheimer for his words of wisdom on 'patient experience', and to all my interviewees for giving up their time for this study.

Chapter 3– The study presented in this chapter was conceived by myself, and undertaken with Dr. Anthony Cox (ARC), Professor Robin Ferner (REF), and Dr. Jan Oyebode (JO), with whom I also published a paper based on this chapter. I am grateful to Oliver Mason (OM), Lecturer and Computational Linguist in the Department of English, University of Birmingham, for undertaking the word frequency analysis of the internet narratives analysed in the study.

Chapter 4– The study presented in this chapter was conceived and undertaken by myself and Dr Una Martin (UM), with whom I also published a paper based on the study. I am indebted to Dr. Martin for her support and advice during the study, and to Rebecca Branch, our Research Assistant, for her invaluable help in data collection. I would also like to thank Louise Beesley, Specialist Nurse in Hypertension, for her guidance in using the research database described in the study, and to our secretary Margaret Webster, for her help in locating clinic letters.

Chapter 5– The final chapter presented in this thesis is my own work, and I am grateful again, to my supervisors, Professor Ferner and Dr Una Martin, for their invaluable guidance.

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Abbreviations

A	ABPM	Ambulatory blood pressure monitoring
	ACE	Angiotensin-converting enzyme
	ADR	Adverse Drug Reaction
	AIDS	Acquired Immune Deficiency Syndrome
	ARB	Angiotensin receptor blocker
B	BC	Beers Criteria
	BHS	British Hypertension Society
	BMI	Body Mass Index
	BP	Blood pressure
	BSA	Body surface area
	cAMP	Cyclic adenosine monophosphate
C	CD8	Cluster of differentiation 8
	CI	Confidence Interval
F	FDA	Food and Drug Administration
G	GFR	Glomerular Filtration Rate
	GP	General Practitioner
H	HIV	Human Immunodeficiency Virus
	HLA	Human Leukocyte Antigen
	HYVET	Hypertension in the Very Elderly Trial
I	IVIg	Intravenous immunoglobulin
M	MHC	Major Histocompatibility Complex
	MHRA	Medicines and Healthcare products Regulatory Agency
N	NHS	National Health Service
	NICE	National Institute for Clinical Excellence
	NSAIDs	Non-Steroidal Anti-inflammatory Drugs
P	PIMs	Potentially inappropriate medications
	PTSD	Post traumatic stress disorder
S	SCARs	Serious cutaneous adverse reactions
	SCORTEN	Severity of illness in TEN
	SJS	Stevens-Johnson Syndrome
	START	Screening to Alert Doctors to Right Treatment
	STOPP	Screening Tool of Older persons' Prescriptions
T	TEN	Toxic Epidermal Necrolysis
W	WCE	White Coat Effect
	WHO	World Health Organisation
Y	YCS	Yellow Card Scheme

1 CHAPTER 1–INTRODUCTION

1.1 Background

Despite their benefits, medicines can cause significant harm due to the occurrence of adverse drug reactions (ADRs). Healthcare professionals have a duty of care to the patients they prescribe medicines to, and should remain vigilant for any harm which may result. Patients themselves are also becoming increasingly aware of the potential harms associated with medicines, and in today's consumer-driven society, often wish to be involved in decisions regarding many aspects of their care, including the medicines they are prescribed. Healthcare professionals, and indeed patients, face numerous challenges when considering ADRs; these include the desire to avoid or prevent ADRs in the first place, recognise ADRs when they do occur, and once recognised, manage them appropriately. The first challenge is to make an assessment of the balance between the benefits and harms of prescribing a medicine, taking into account the strength or quality of the available evidence. Some ADRs are avoidable or preventable, for example, those resulting from prescribing a drug that is contraindicated or is inappropriate for a patient's clinical condition, and those that occur due to inadequate monitoring of the patient whilst taking the drug (Schumock and Thornton 1992). In addition, certain groups of patients, such as the very elderly, have an increased susceptibility to ADRs, and this will in fact be the focus of part of this thesis. Of course, there are many ADRs which cannot be predicted or anticipated, as I will discuss later.

ADRs may go unrecognised when they do occur, and this may be due to the fact that they have a wide variety of clinical presentations, can affect any bodily system, and thus, may

mimic any disease process or illness. Misdiagnosis may therefore result. In addition, poor - communication between healthcare professionals and patients regarding the potential harms of a prescribed drug may result in late detection of ADRs. Both misdiagnosis and late detection of ADRs may result in a delay in appropriate management, which may involve withdrawal of the offending drug. The consequences of this may be dire, particularly for serious ADRs.

ADRs may be considered a major public health concern. They occur frequently, are a common cause for hospital admission, and are associated with significant patient morbidity, mortality, and cost, as I will describe later in this chapter. But what is the burden of ADRs in terms of their impact on patients' lives? What are patients' experiences and views regarding ADRs, and what concerns do those who have experienced ADRs have? Can these areas be explored to help us improve the management of patients experiencing ADRs? These are questions which are currently unanswered, and which I aim to explore through the work presented in this thesis.

1.2 Adverse Drug Reactions (ADRs)

1.2.1 Definitions of ADRs

A number of definitions for adverse drug reactions (ADRs) currently exist. The World Health Organisation (WHO) defines an ADR as "A response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function" (WHO 1972).

Edwards and Aronson (2000) argue that many of the definitions that exist are either vague in their use of terms such as 'noxious' (as is the case with WHO's definition) or exclude error as a source of adverse effects; they define an ADR as "An appreciable harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product." In addition, they define a serious ADR as "an ADR that at any dose, results in death, requires hospital admission or prolongation of existing hospital stay, results in persistent or significant disability/incapacity, or is life-threatening" (Edwards and Aronson 2000). ADRs discussed in this thesis will be based on these definitions.

Finally, international terminology for the coding of ADRs, known as WHO's Adverse Reaction Terminology (WHO-ART) is also currently accepted. This terminology has a four tier hierarchical structure, consisting of adverse reaction terms related to: i) System-organ classes (or body organ groups); ii) High level terms (for grouping preferred terms); iii) Preferred terms (principle terms for describing ADRs); and iv) Included terms (synonyms to

preferred terms). In addition to this, WHOART also highlights some terms as 'Critical Terms', which indicates the seriousness of the ADR (WHO Collaborating Centre for International Drug Monitoring 1992).

1.2.2 Classification of ADRs

ADRs have previously been classified into two main types; type A reactions which are dose-dependent reactions and are predictable from the known pharmacokinetics and pharmacodynamics of the drug, and type B reactions which are not dose-dependent and are idiosyncratic (Rawlins and Thompson 1977).

In some cases however, it can be difficult to decide whether an ADR belongs to one class or another, as a reaction may be both dose-related and idiosyncratic. One example of this is constipation due to opiate drugs. This ADR may be categorised as a Type A reaction as it is dose-dependent, but as it cannot be pharmacologically predicted in all patients, it could also be classed as a type B reaction. In addition, other ADRs are dependent not only on dose, but also on the duration of treatment, which is not taken into account in the above described classification system (Aronson and Ferner 2003).

Subsequently, further types of reactions were added to the classification: type C (related to dose and time), type D (delayed reactions), type E (withdrawal reactions), and type F (failure of therapy) (Aronson 2002).

Despite the addition of further types, this classification only takes into account the properties of the drug, and not the properties of the reaction (e.g. its severity) or properties of the individual (e.g. genetic susceptibility). Aronson and Ferner (2003) therefore proposed a three

dimensional classification system based on dose-relatedness, timing, and patient susceptibility (DoTS) to overcome the shortcomings of previous systems, and for the purpose of this thesis, ADRs will be described using this system.

In terms of dose-relatedness, ADRs can be divided into those that occur at supratherapeutic doses (toxic effects); reactions that occur at standard therapeutic doses (collateral effects); and reactions that occur at subtherapeutic doses in susceptible patients (hypersusceptibility reactions).

ADRs related to time are subdivided into time dependent and time independent reactions. Time independent reactions can occur at any time during treatment. They typically occur either when the concentration of the drug at the site of action changes or when the pharmacological response is altered without a change in concentration. Time dependent reactions can be divided into six subtypes; i) rapid reactions (e.g. red man syndrome with rapid administration of vancomycin); ii) first dose reactions (e.g. hypotension after administration of the first dose of an angiotensin-converting enzyme inhibitor), iii) early reactions (i.e. ADRS to which patients develop tolerance to over time), iv) intermediate reactions (e.g. delayed hypersensitivity reactions), v) late reactions (e.g. ADRs where the risk increases with continued or repeated exposure), and vi) delayed reactions (ADRS often occurring some time after exposure, e.g. teratogenesis).

Finally, ADRs related to patient susceptibility are those which differ among members of an exposed population, as for example, is the case with carbamazepine-induced Stevens–Johnson syndrome in individuals of Han Chinese ethnicity with the human leukocyte antigen *HLA–B*1502* genotype (Chung et al. 2004), which is discussed later in this thesis.

1.2.3 Epidemiology of ADRs

The impact of ADRs on patient morbidity and mortality is high, and is associated with a significant financial burden on current healthcare systems. A meta-analysis of 39 prospective studies from US hospitals showed that the overall incidence of serious ADRs in hospitalised patients was 6.7% and 0.32% for fatal ADRS. The analysis was undertaken for both ADRs occurring whilst in hospital, and ADRs causing admission to hospital, and the authors defined serious ADRs as those that required hospitalisation, were permanently disabling, or resulted in death (Lazarou et al. 1998). Although the meta-analysis described was flawed due to multiple sources of heterogeneity amongst studies, including differences in populations, surveillance techniques, and ADR definitions, subsequent large prospective studies have also confirmed that ADRs are a significant problem.

A subsequent UK based prospective study, for example, analysed data from 18820 patients admitted to hospital over a six month period, and showed a 6.5% prevalence of ADRs, with the ADR directly leading to the admission in 80% of cases, and an overall fatality of 0.15%. Of significance, most ADRs were classed as definitely or possibly avoidable. Drugs most commonly implicated in causing these admissions included low dose aspirin, diuretics, warfarin, and non-steroidal anti-inflammatory drugs (NSAIDs) other than aspirin, with the commonest reaction being gastrointestinal bleeding. The projected annual costs of such admissions were estimated to be around £466m, emphasising the huge burden on the NHS (Pirmohamed et al. 2004).

Another prospective analysis of hospital inpatients found that a high incidence of ADRs also occurred following admission during the patients' stay in hospital, and around half of these were definitely or possibly avoidable. Those who experienced ADRs were more likely to be

older, female, taking a larger number of medications, and had a longer length of stay than those who did not. ADRs directly resulted in an increase in the length of inpatient stay in 26.8% of patients (Davies et al. 2009).

1.2.4 Preventable ADRs

In general, an ADR may be deemed preventable or avoidable if it is an anticipated reaction, and if certain actions can prevent its occurrence. Many definitions of preventable ADRs in the literature exist.

Hallas et al (1990) for example, proposed definitions focusing on the avoidability of ADRs, i.e. whether an ADR could have been avoided by appropriate measures taken by healthcare professionals, and classed ADRs as 'Definitely avoidable', 'Possibly avoidable', 'Not avoidable', or 'Unevaluable' as can be seen in table 1-1.

Schumock and Thornton (1992) also proposed criteria for determining the preventability of ADRs, consisting of a series of detailed questions about the ADR, as can be seen in Table 1-2. Many of the studies described in this thesis have used the criteria proposed by either Hallas et al or Schumock et al to assess avoidability of ADRs.

Table 1-1: Hallas criteria for avoidability of ADRs (Hallas et al. 1990)

Definition of ADR	**Description**
Definitely avoidable	The drug event was due to a drug treatment procedure inconsistent with present-day knowledge of good medical practice or was clearly unrealistic, taking the known circumstances into account.
Possibly avoidable	The prescription was not erroneous, but the drug could not have been avoided by an effort exceeding the obligatory demands.
Not avoidable	The drug event could not have been avoided by any reasonable means, or it was an unpredictable event in the course of a treatment fully in accordance with good medical practice.
Unevaluable	The data for rating could not be obtained or the evidence was conflicted.

Table 1-2: Criteria for determining the preventability of ADRs (Schumock & Thornton 1992)

Answering "Yes" to one or more of the following questions, implies that the ADR is preventable:

1. Was the drug involved inappropriate for the patient's clinical condition?
2. Was the dose, route, or frequency of administration inappropriate for the patient's age, weight, or disease state?
3. Was required therapeutic monitoring or other necessary laboratory tests not performed?
4. Was there a history of allergy or previous reactions to the drug?
5. Was a drug interaction involved in the ADR?
6. Was a toxic serum drug concentration (or laboratory monitoring test) documented?
7. Was poor compliance involved in the ADR?

It is important to note however, that many of the criteria and algorithms currently in use to assess preventability of ADRs including those described, may have limited reliability and validity, as shown in a recent systematic review (Hakkarainen et al. 2012). In addition, a number of studies and reviews focusing on preventable ADRs have failed to provide definitions for preventable ADRs or provided definitions that were not relevant, which may throw doubt on the conclusions drawn from such studies (Ferner and Aronson 2010).

But which drugs most frequently cause preventable ADRs? A systematic review of prospective observational studies found that the median percentage of preventable drug-related admissions to hospital was 3.7% with the majority involving antiplatelet agents

(16%), diuretics (16%), non-steroidal ant-inflammatory drugs (NSAIDs) (11%) or anticoagulants (8%) (Howard et al. 2007).

1.2.5 The elderly and ADRs

The elderly are a group who are particularly susceptible to ADRs, which are a major cause of admission to hospital in this group. An Italian prospective study of 1756 patients aged 65 years and above, evaluated the prevalence, clinical characteristics and avoidability of ADR-related hospital admissions in the elderly. They found that almost 6% of hospital admissions in this age group were ADR-related, of which at least 45% were avoidable. Gastrointestinal disorders (47.1%), platelet, bleeding, and clotting disorders (19.6%), and cardiovascular disorders (12.7%) were the most frequent ADRs, with NSAIDs (23.5%), oral anticoagulants (20.6%), low-dose aspirin (13.7%), and digoxin (12.7%) most frequently involved (Franceschi et al. 2008).

The majority of total admissions related to ADRs also occur in the elderly. An epidemiological study from the Netherlands showed that over two thirds of admissions related to ADRs over 1981-2007, occurred in patients aged 60 years and above, despite the fact that this age group constituted only 17.6% of the population (Hartholt et al. 2010). The study also found that ADR-related admissions in the elderly showed a rapidly increasing trend over the last three decades, with the commonest ADRs including bleeding, gastrointestinal symptoms, and anaemia.

Another similar cross-sectional study of elderly patients admitted to hospital found that a severe ADR (which they defined as an ADR which was potentially life-threatening or led

directly to hospital admission), was experienced by 24% of patients aged 70 years and above admitted to hospital (Mannesse et al. 2000).

ADRs in the elderly are also commonly observed in the community and in nursing homes. A retrospective cross sectional analysis of 2185 elderly patients in general practice showed that the incidence of ADRs was 5.7%, and that polypharmacy was more frequent in the elderly who experienced adverse effects. Unlike data from hospital based studies however, the study showed that most of the ADRs observed in general practice were minor. Nausea was the most frequently occurring ADR and was associated with antibiotics and antidepressant use. Unsurprisingly, elderly patients who experienced ADRs consulted their general practitioner more often than those without (Veehof et al. 1999).

Another cohort study of all long-term residents of 18 community based nursing homes in the US, found that during 28839 resident-months of observation, there were 546 ADRs, and 188 potential ADRs; 51% were thought to be preventable (Gurwitz et al. 2000). The cost of these events is significant and one community-based study estimated that 1000 older adults would have annual costs of $65,631 related to ADRs, $27,365 of which would be associated with preventable events (Field et al. 2005).

It is clear that ADRs have a significant impact in the elderly, but as we have seen, some medicines are more likely to cause ADRs in the elderly than others. Antihypertensive agents are one such group of medicines, and diuretics and calcium channel blockers are most frequently implicated (Onder et al. 2002). I therefore aim to explore the impact of ADRs secondary to antihypertensive agents in Chapter 4 of my thesis.

1.2.6 Patient reporting of ADRS

The monitoring of ADRs through pharmacovigilance may contribute to patient safety. Pharmacovigilance has been defined as 'the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems' (World Health Organisation 2002).

Clinical trials for new drugs can help identify ADRs associated with them. Spontaneous reporting of ADRs is another method of pharmacovigilance. Many countries have set up national spontaneous reporting systems or agencies for ADRs, and in the UK, this is undertaken through the Yellow Card Scheme (YCS) (Rawlins 1988). Yellow Card reports are submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) either by post, telephone, or via the internet. Information submitted is then recorded and reviewed by the MHRA, so that concerns regarding potential adverse effects from medicines can be identified and followed up.

Until relatively recently, ADRs could only be reported to such agencies by healthcare professionals. Over the past decade however, the reporting of ADRs directly by patients has been established in at least 46 countries including the UK, the US, Australia, and the Netherlands (Avery et al. 2011;van Grootheest et al. 2003).

Although the majority of ADRs are reported by healthcare professionals, patient reporting may be valuable for a number of reasons. Firstly, clinical trials for new drugs are not able to identify all ADRs associated with them, as trials often exclude patients with concomitant disease or drug therapy. In addition, the study population may not be large enough to detect

rarer ADRs, and trials may not be long enough to detect ADRs associated with long term use. Under-reporting by healthcare professionals is also a significant problem both in the community and in secondary care (Anderson and Choonara 2010;Hazell and Shakir 2006;Moride et al. 1997); hence reporting by patients may increase the rate of ADR detection. It is also important to note that patient involvement in the reporting of ADRs could be considered as part of a wider phenomenon of involving patients in interventions or initiatives to help promote their own safety. The concept of patient involvement in healthcare is not unique to the area of patient safety, and there is in fact a broad interest and literature base for patient involvement strategies in many aspects of healthcare (Hall et al. 2010).

1.2.7 Quality of patient reports of ADRs

Although an ADR is first evident to the patient in many cases, patient reporting relies on the ability of the patient to make an association between the symptom and the drug, and to be able to distinguish the symptom from symptoms of other illnesses. Although it could be argued that lay people might lack this ability, the available evidence points to the contrary. Data from a post-marketing surveillance study of ambulatory patients, for example, showed that patients appear to be capable of correctly discriminating probable adverse drug reactions from other adverse clinical events. Interestingly, this discrimination was better when patients were reporting adverse clinical events spontaneously than when they were probed for recall in a systematic inquiry (Fisher and Bryant 1990).

But are patients able to provide information of the quality required to accurately diagnose and classify an ADR? There is some evidence to suggest that they can. A questionnaire-

based study, for example, showed that patients are able to describe ADRs experienced, reasonably well in terms of the elements required to diagnose and classify an ADR, although some elements were more likely to be included in spontaneous descriptions of the ADR than others (Dewitt and Sorofman 1999). The study explored whether the general population inherently employed a cognitive model that represents ADRs in terms of 5 common prototype elements, required to diagnose an ADR: i) identity (label and symptom); ii) cause; iii) time line; iv) consequences; and v) cure. Patients were asked to provide a 'narrative' of an ADR they remembered best followed by closed questions regarding the ADR. Each was then coded for the potential elements of a prototype. Ninety-eight percent of respondents' descriptions mentioned the symptoms associated with the ADR. Forty-four percent of those who reported an ADR spontaneously mentioned the cause of the reaction by naming the implicated drug or drug class, and 94% provided this information when directly asked. Only 10% however included a time line for the reaction, 24% the consequences of the ADR, and 3% the 'cure' of the ADR (e.g. whether or not the culprit drug was withdrawn or not) (Dewitt & Sorofman 1999).

Symptoms reported as ADRs by patients do, in fact, have a high likelihood of being caused by the suspected drug. Another questionnaire-based study of patients prescribed one of nine recently marketed 'black triangle' drugs, asked respondents to identify any symptoms experienced over the previous year which they thought could be due to the black triangle drug used. They found that 71% of symptoms reported as ADRs could be classed as probable or possible ADRs. Interestingly, they also found that patients reporting ADRs from certain drug classes such as antidepressants for example, were more likely to be caused by the drug (Jarernsiripornkul et al. 2002). Another study by the same authors, compared doctor and

patient reporting for new drugs, and found that patients often reported a higher number of ADRs compared to healthcare professionals, and at least 76% of these could be classed as probable or possible ADRs (Jarernsiripornkul et al. 2009).

The important contribution of patient reports of ADRs was shown in a review of patient reporting systems from six countries, where possible new ADRs that had not previously been reported by healthcare professionals were identified (Blenkinsopp et al. 2007).

In addition, a major national survey commissioned by the National Institute for Health Research Health Technology Assessment programme, evaluated the impact of patient reporting of ADRs by analysing reports of suspected ADRs from the UK Yellow Card Scheme (YCS) and compared reports from patients and healthcare professionals. Using both quantitative (questionnaire-based) and qualitative (interview-based) methods, they found that compared to healthcare professional reports of ADRs, patient reports to the YCS contained a higher number of suspected ADRs per report, and described reactions in more detail. Although the proportion of reports categorised as 'serious' was similar, the types of drugs and reactions reported were different. Patient reports were also 'richer' and more detailed in their descriptions of ADRs, and more often described the effects on patients' lives than reports from healthcare professionals. The addition of patient reports generated new signals when combined with healthcare professional reports; in particular, they helped identify 47 new serious reactions not previously included in the 'Summaries of Product Characteristics' of the suspected drugs (Avery et al 2011).

1.2.8 Motivation for patient reporting of ADRs

But why might patients wish to report an ADR? Around half of the patients who reported to the Netherlands Pharmacovigilance Centre Lareb in the first 6 months of it starting its patient reporting website, were motivated to do so as they felt that their healthcare professional did not listen to their complaint about a possible ADR, or the patient was not convinced that he or she would report their experience (van Grootheest and de Jong-van den Berg 2004). This emphasises the perceived lack of sufficient attention given by healthcare professionals to ADRs experienced by the patient, and there is in fact evidence to suggest that this perception may be true. In one Thai study of outpatients, for example, patients identified 249 symptoms, of which the pharmacist assessed 190 (76%) as probable or possible ADRs. Only 26 symptoms however, were noted in the outpatient records by healthcare professionals, and only five reported on ADR forms (similar to UK Yellow cards), although most patients claimed to have informed doctors about them (Jarernsiripornkul et al 2009). Avery et al (2011) also found that the majority of patient reporters to the Yellow Card Scheme they surveyed (n= 1098; 80.6%), stated that reporting the ADR had been their own idea, with 56 patients (4.1%) stating that a healthcare professional had refused to submit the report on their behalf. Patients also indicated their expectations of reporting, including getting feedback from the MHRA regarding the ADR and the drug that caused it, and wanting to know whether any investigation or action would take place as a result of the report, such as informing manufacturers or healthcare professionals.

Despite this, it must however be borne in mind that some patients may not voice their concerns regarding ADRs directly to their healthcare professionals, which may thus prevent

them being addressed. This may, for example, be due to the fact that healthcare professionals have done little to facilitate the exploration of patients' real concerns within consultations, or that patients decide not to mention them for fear of 'wasting doctor's time'. Such concerns regarding ADRs may thus remain 'unvoiced', emphasising the importance of good communication both by healthcare professionals and by patients (Barry et al. 2000).

1.2.9 Public perceptions of harms and benefits of medicines

Public perceptions of harms and benefits of medicines in general have also been explored. A survey commissioned by the MHRA of the general public using focus groups and in-depth telephone interviews to collect data, found that confidence in medicines seemed to stem from an overall confidence in doctors. Older participants formed opinions on medicines based on personal experience, or experience of friends and family, and were generally positive towards medicines as they saw them as 'vital'. Some younger participants had a generally cautious approach to medicines; they were worried about becoming 'dependent' on them, with some expressing concerns about the side-effects of painkillers. However, some of them described taking particular medicines despite being aware of the side-effects; they were not necessarily weighing up the benefits against the risks, but rather focusing on any immediate benefit. Finally participants found 'risk' hard to conceptualise; they generally had few concerns as they trusted what their doctor was prescribing.

A quantitative analysis of almost 2000 adults during the same study, did however reveal that almost half always weighed up the risks and benefits of a medicine before deciding to take it or not, whereas on the other extreme, one in seven said that they never did this. Almost nine in ten adults trusted doctors to provide accurate information about the risks and benefits of

medicines; among the least trusted sources were pharmaceutical companies and government organisations (Ipsos MORI and MHRA 2006).

The general public also appear to have different views regarding what they would do if they developed an ADR. In a questionnaire-based study of adults attending a family medicine clinic, the majority (69%) of participants stated that they would stop taking the offending drug as a response to the onset of an ADR, and 71% of the total sample indicated that they believed an ADR would occur within minutes to hours of drug administration. The majority of respondents (93%) indicated that they would contact a physician regarding an adverse drug effect (Dewitt and Sorofman 1999).

1.2.10 Patient experience of ADRs

I have, thus far, discussed ADRs in terms of their definitions, epidemiology, and their reporting, both by healthcare professionals, and of particular relevance to my thesis, by patients themselves. It is clear from previous research undertaken, that ADRs have a marked impact both on patient morbidity and mortality. It is also clear that patients may play an important role in the reporting of ADRs. It is surprising, therefore, that the experiences of patients who have suffered the effects of serious ADRs have not been previously explored. In addition, the perceptions, views, and concerns of those who have experienced serious ADRs are yet to be investigated.

But why might the study of patient experience of ADRs be useful? To answer this question, we must firstly understand that the study of patient experience of any illness can inform

improvements in the care provided by healthcare professionals for that illness. In particular, studying the experiences and views of patients can help us provide patient-centred care, which is defined as 'providing care that is respectful of and responsive to individual patient preferences, needs, and values, and ensuring that patient values guide all clinical decisions' (Committee on Quality of Health Care in America 2001). This is, in fact, the cornerstone of today's NHS, which, as outlined in the recent Department of Health White Paper 'Equity and excellence: Liberating the NHS', should focus on continuously improving those things that really matter to patients, thus putting the patient and their experience at the heart of quality improvement (Department of Health 2010).

Recent hospital data from a national patient survey also suggests that patient-reported experiences and the fulfilment of patient expectations are significantly associated with the overall satisfaction that patients have regarding their care (Bjertnaes et al. 2012).

With this in mind, I aim to explore the experiences and views of those who have suffered the effects of serious ADRs in Chapters 2 and 3 of this thesis. I have chosen to focus in particular on drug-induced Stevens-Johnson syndrome and Toxic epidermal Necrolysis, as they are amongst the most serious and life-threatening ADRs and the causal relationship between a drug and the condition is often clear.

2 CHAPTER 2–A QUALITATIVE STUDY OF THE EXPERIENCES OF SURVIVORS OF STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS, AND THEIR ATTITUDES TO MEDICATIONS AND ADVERSE DRUG REACTIONS

I have published a paper related to this chapter**:** Butt TF, Cox AR, Lewis H, Ferner RE. Patient Experiences of Serious Adverse Drug Reactions and their Attitudes to Medicines. A qualitative study of survivors of Stevens-Johnson syndrome and Toxic Epidermal Necrolysis in the UK. *Drug Safety* 2011; 34(4): 319-328.

(See Appendices)

2.1 Introduction

Adverse skin reactions to drugs are a common problem in daily medical practice, and are amongst the most frequently reported ADRs in epidemiological studies and spontaneous reporting systems. The Boston Collaborative Drug surveillance programme analysed data from 15,430 consecutive medical inpatients, and found that around 2.2% had drug-induced skin reactions (Bigby et al. 1986). Another epidemiological study in Switzerland over a 20-year period also had similar findings, with cutaneous ADRs in 2.7% of hospitalised patients (Hunziker et al. 1997).

An analysis of ADRs reported spontaneously to surveillance systems in four Italian regions found that 44.7% of all reported ADRs were adverse skin reactions to drugs, with the highest number of cutaneous ADRs due to antimicrobials, followed by analgesics and Non-steroidal anti-inflammatory drugs (NSAIDs) (Naldi et al. 1999).

A subsequent review of major studies containing primary data on the rates of cutaneous reactions to drugs, also confirmed that antibiotics were the commonest culprits, and found that morbilliform (maculopapular) and urticarial rashes were the commonest cutaneous reactions (Bigby 2000).

Fortunately, the majority of cutaneous ADRs are minor, with only 17% of cutaneous ADRs classed as serious based on the WHO critical term list for adverse reactions. (Naldi et al. 1999). Although serious cutaneous adverse reactions (SCARs) are rare, they are, however, associated with a high morbidity and mortality rate, and prompt recognition and treatment is important. Among the most serious types of reactions are Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). These are acutely life-threatening cutaneous ADRs characterised by epidermal necrosis, extensive epidermal detachment, mucous membrane erosion, and severe constitutional symptoms**.**

2.1.1 Stevens- Johnson syndrome and Toxic epidermal necrolysis

Stevens-Johnson syndrome (SJS) was first described in 1922 by American paediatricians Albert Stevens and Frank Johnson, as an acute mucocutaneous syndrome in two young boys. The condition was characterised by fever, severe purulent conjunctivitis, severe stomatitis, and extensive mucosal necrosis. Both cases had been initially diagnosed by a primary care physician as measles and one case subsequently, as erythema multiforme. Both children survived the illness, but one was left completely blind. The cases were presumed to have an infectious aetiology, but this could not be definitively proven (Stevens and Johnson 1922).

In 1956, Alan Lyell described four patients who developed a skin eruption resembling scalded skin. The condition was described as resulting in the formation of blisters and 'loosening of skin which peeled off in shreds', leaving tender raw surfaces liable to bleeding. He called this condition toxic epidermal necrolysis or TEN, and it subsequently also became known as Lyell's syndrome. In two cases the disease had been recurrent, and in one case, the patient died as a result. In at least two cases, a drug cause was suspected (Lyell 1956). Only when further cases of TEN and SJS were reported in the years following Stevens', Johnson's, and Lyell's publications, did it become clear that many cases were indeed drug-induced, and that certain drugs such sulphonamides, barbiturates, and antiepileptics were frequent triggers.

2.1.2 Epidemiology of SJS and TEN

SJS and TEN are rare. The incidence of TEN is estimated at 0.4 to 1.2 cases per million person-years (Chan et al. 1990;Roujeau et al. 1990;Schopf et al. 1991) and of SJS, at 1 to 6 cases per million person-years (Chan et al. 1990;Schopf et al. 1991).

The overall incidence of both SJS and TEN has been found in one population-based study to be higher in patients aged less than 20 years, and greater than 65 years (7.0 per 10^6 person-years and 9.0 per 10^6 person-years respectively), compared to patients aged 20−64 years (1.8 per 10^6 person-years). However this study also included patients with erythema multiforme (a condition which is now recognised as a separate entity) (Chan et al. 1990). In another epidemiological study from West Germany, the incidence of TEN alone was found to be greater in the elderly (average age of onset 63 years), with SJS occurring more frequently in

younger patients (average age of onset 25 years). In this study, 88% of cases could be directly attributed to a drug cause (Schopf et al. 1991).

Despite their rarity, these conditions may be fatal or significantly disable previously healthy individuals. The medical and economic impact of these ADRs is therefore greater than would be expected on the basis of incidence alone.

Over a hundred drugs have been implicated as a cause of SJS and TEN. The commonest drugs implicated include sulphonamides, anticonvulsant agents, non-steroidal anti-inflammatory drugs, and allopurinol. Roujeau et al (1995) undertook a case-control study to quantify the risks of SJS and TEN associated with the use of specific drugs, and collected data through surveillance networks in France, Germany, Italy, and Portugal. Drug use before the onset of the disease in 245 patients hospitalised as a result of SJS or TEN, was compared to that in 1147 controls (patients hospitalised for other acute conditions). They found that the relative risk of SJS or TEN was increased with the use of a number of drugs, the commonest being sulfonamides. Other drugs associated with SJS and TEN included aminopenicillins, cephalosporins, carbamazepine, phenytoin, and allopurinol. (See Table 2-1) They also found that for many drugs, the risk of SJS and TEN was highest in the first few weeks of use. (Roujeau et al. 1995)

Table 2-1: Estimates of excess risk with drugs associated with SJS and TEN (Adapted from Roujeau et al 1995)

Drug	*Cases (n=245)*	*Controls (n=1147)*	*Relative Risk*	*Excess Risk*
Sulfonamides	32	1	172	4.5
Trimethoprim-sulfamethoxazole	22	0	160	4.3
Carbamazepine	13	0	90	2.5
Phenytoin	8	0	53	1.5
Allopurinol	11	1	52	1.5
Cephalosporins	14	3	14	0.4
Tetracyclines	5	4	8.1	0.2
Aminopenicillins	15	12	6.7	0.2

Another multinational case-control study (EuroSCAR) found that allopurinol, a xanthine oxidase inhibitor used in the treatment of gout, was the commonest cause of SJS and TEN in Europe and Israel, with daily doses equal to or greater than 200 mg (Halevy et al. 2008). Although drugs are assumed or identified as the main cause of SJS and TEN in the majority of cases, infections caused by *Mycoplasma pneumoniae* and Herpes simplex virus infections are well documented causes, particularly in children, alongside rare cases in which the aetiology remains unknown (Harr and French 2010).

Other diseases may have an impact on the incidence of TEN; individuals infected with the Human immunodeficiency virus (HIV), for example, have a higher risk of developing TEN than the general population (Saiag et al. 1992). There have also been case reports of TEN observed in the context of acute graft-versus-host disease after bone marrow transplantation (Arvidson et al. 2007).

In addition, genetic factors and ethnicity may also be associated with an increase in the risk of developing SJS and TEN. Some studies, for example, have shown an association between certain human leukocyte antigens (HLAs) and SJS and TEN. A strong association between *HLA-B* 1502* and carbamazepine-induced SJS has been shown in the Han Chinese

population (Chung et al 2004), and a possible association between *HLA-B*1511* and carbamazepine-induced SJS in Koreans (Kim et al. 2011). A systematic review and meta-analysis found a strong and significant association between *HLA-B*5801* and allopurinol-induced SJS and TEN, with similar findings for both Asian and non-Asian populations (Somkrua et al. 2011). It has been postulated that the HLA molecule is directly involved in antigenic drug presentation resulting in T cell activation (see 2.1.4), although the precise mechanism is still unknown (Chung et al. 2007).

As those with certain genetic factors, ethnicity, or illnesses have a higher risk of developing SJS or TEN, these ADRs could be classed as hypersusceptibility reactions in these groups using the DoTs (Dose-relatedness, timing, and patient susceptibility) classification of ADRs (Aronson & Ferner 2003) as discussed in Chapter 1. It is important to note however, that in other cases of SJS and TEN (which are the majority), there is no way of predicting whether a patient is at increased risk of developing the ADR.

2.1.3 Clinical features of SJS and TEN

Although the nosology and specific diagnostic criteria for SJS and TEN remain controversial, certain clinical features help define these conditions. The similarities in both the histopathological findings and the drugs responsible for these two conditions, suggest that they both form part of a single spectrum of disease, differing only by their extent of skin detachment. SJS affects less than 10% of body surface area (BSA) with discrete maculopapular lesions and erosions, and has a mortality rate of 1-5%, whereas TEN affects greater than 30% of BSA with sheet-like erosions, and a higher mortality rate of 30-40%.

Cases involving between 10% and 30% of BSA are classed as SJS-TEN overlap syndrome (Bastuji-Garin et al. 1993;Breathnach 2010;French 2006).

Historically, erythema multiforme, a condition involving macular, papular, or urticarial lesions, as well as classical 'target lesions', was also considered to be part of the same spectrum. More recently, a re-evaluation of this concept has led to the recognition of this condition as a separate entity often related to infections, and only occasionally (10% of cases) to drugs (Breathnach 2010).

Drug-induced SJS and TEN typically present 1 to 3 weeks after exposure to the suspected drug. Initial symptoms may be unspecific and include symptoms of fever, stinging eyes, and discomfort on swallowing. Typically, these symptoms precede cutaneous manifestations by a few days (Gerull et al. 2011).

Early sites of cutaneous involvement include the presternal region of the trunk, the face, and the palms and soles. The morphology of early skin lesions include erythematous macules with purpuric centres which have a tendency to rapidly coalesce (Harr and French 2010;Gerull et al. 2011).

Three to five days after the onset of symptoms, large areas of epidermal detachment develop. Macules progress to large blisters with subsequent epidermal detachment, without any involvement of the hair. Separation of the epidermis progresses and leads to large denuded areas. Large wound areas leads to extreme pain, massive loss of fluid and protein, bleeding, evaporative heat loss, with subsequent hypothermia and infection. The extent of skin involvement is a major prognostic factor. Only necrotic skin, which is already detached (e.g.

blisters and erosions) or detachable skin (Nikosky sign positive) should be included in the evaluation of the extent of skin involvement. The Nikolsky sign is positive if tangential mechanical pressure on several erythematous areas induces epidermal detachment (Harr and French 2010;Gerull et al. 2011).

The complications of TEN and extensive thermal burns are similar. Massive transdermal fluid losses (3–4 litres daily in adults with half their body surface area involved) occur with associated electrolyte imbalance and pre-renal failure. Bacterial colonisation of the skin and decreased immune responsiveness increase the likelihood of sepsis (Roujeau and Stern 1994).

Mucous membrane involvement occurs a few days after the initial symptoms. Erythema and erosions of the buccal, genital, or ocular mucosa occurs in greater than 90% of patients, and in some cases, the respiratory and gastrointestinal tracts are also affected (Harr and French 2010).

Eye involvement at the onset of disease is frequent, and can range from acute conjunctivitis, eyelid oedema, and ocular discharge, to conjunctival pseudomembrane formation, symblepharon (adhesion of the conjunctiva covering the cornea to the overlying eyelid), corneal ulceration, and endophthalmitis (Gueudry et al. 2009).

Gastrointestinal involvement frequently occurs in the mouth and oesophagus, but can also occur in the small bowel and colon, causing impaired alimentation, and necessitating the need for enteral nutrition (Roujeau & Stern 1994).

Respiratory involvement can result in large ulceration and epithelial necrosis of the bronchial tree. Consequences include pulmonary oedema and progressive respiratory failure.

Intubation and ventilation may be required and is associated with a higher mortality (Gerull 2011).

Other organ manifestations occur rarely, but renal involvement with glomerulonephritis, pancreatitis, and liver involvement with hepatocellular necrosis or cholestasis have been reported (Gerull 2011).

2.1.4 Pathogenesis

Although the pathogenesis of SJS/TEN is not fully understood, it is believed to be an immune-mediated ADR, as re-challenging an individual with the same drug or exposure to another drug with cross-reactivity (e.g. cephalosporins and carbopenems), can result in a rapid recurrence of the disease (Ciaccio and Saltoun 2008;Paquet et al. 2002). Histopathological analysis of SJS/TEN skin lesions also support an immunological basis for these conditions. Keratinocyte apoptosis followed by necrosis has been shown to be the pathological basis of the widespread epidermal detachment seen in SJS and TEN. Cytotoxic T lymphocytes are thought to play a major role in the initial phase of the reaction, as in the early phase of the disease, blister fluid contains mainly cytotoxic CD8+ T lymphocytes, suggesting that a major histocompatibility (MHC) drug presentation leads to clonal expansion of these cells (Harr and French, 2010).

Blister T lymphocytes from patients have also been shown to exert drug specific cytotoxic activity against keratinocytes, further supporting an immunological basis for the disease (Nassif et al. 2004). The involvement of CD8 T lymphocytes, thus suggests some form of delayed hypersensitivity reaction. However, how a culprit drug given to a patient regulates the function of these cells is yet unknown.

2.1.5 Differential diagnoses

Histological examination including direct immunofluorescence analysis of a skin biopsy is important to rule out differential diagnoses including other serious cutaneous ADRs such as such as generalised bullous fixed drug eruption (GBFDE), acute generalised erythematous

pustulosis (AGEP), hypersensitivity syndrome (HSS) (Bachot and Roujeau 2003;Mockenhaupt 2009), bullous erythema multiforme, which may or may not be drug-related (Auquier-Dunant et al. 2002), and also other conditions which may resemble SJS and TEN such as autoimmune blistering diseases, and staphylococcal scalded skin syndrome (Mockenhaupt 2009; Bachot et al 2003).

2.1.6 Management of SJS and TEN

The management of SJS and TEN is mainly supportive and may require intensive care. Patients often require admission to specialised centres such as burn trauma centres, which are embedded in a critical care infrastructure and offer appropriate treatment of such large cutaneous defects.

Direct admission to such units, is however unusual, and patients are often admitted to regional medical or dermatological departments (Struck et al. 2010). Such patients should be referred to specialist regional burns units early, as there is evidence to suggest that those who are have a better chance of survival (Mcgee and Munster 1998).

A number of studies and reviews have been undertaken to explore the best management of patients admitted acutely with SJS and TEN (Fromowitz et al. 2007;Roujeau and Bastuji-Garin 2011;Schneck et al. 2008;Struck et al. 2010;Teo et al. 2009).

A major goal of supportive care is resuscitation and cardiovascular stabilisation with intravenous fluids and catecholamine therapy if necessary, to maintain sufficient mean arterial blood pressure required for adequate tissue oxygenation and tissue perfusion.

As thermoregulatory mechanisms are impaired with skin loss, there is a significant risk of hypothermia, and this can be avoided by keeping the environmental temperature above 30° C and with the use of heat shields or lamps (Struck et al 2010).

Enteral nutrition is often required as previously discussed, and should be maintained with a hypercaloric diet. Strict sterile nursing may reduce the risk of hospital acquired infections, and frequent systemic and local microbial surveillance is crucial to antimicrobial therapy management.

Due to the large wound surfaces, an initial therapy similar to that used for second degree burns is the method of choice. Large, tight cutaneous blisters should be aspirated, and the sloughed epidermis should be removed (Struck et al 2010).

Patients are at risk of severe bleeding from involved mucosa, and transfusion with red cells and plasma products, may be required.

Prompt withdrawal of the suspected culprit decreases mortality, as shown by a 10-year observational study; the earlier the causative drug is withdrawn, the better the prognosis, and patients who are exposed to causative drugs with long half lives have an increased risk of dying (Garcia-Doval et al. 2000).

As SJS and TEN are believed to be immune-complex-mediated disorders, immunomodulatory therapy with steroids and/or intravenous immunoglobulin therapy are treatments considered for SJS and TEN, but as there is limited evidence to support their efficacy, they remain controversial. A retrospective analysis of data collected from 281 patients with SJS and TEN from the prospective EuroSCAR study showed that neither intravenous immunoglobulin (IVIg) therapy nor corticosteroids were associated with a

significant effect on mortality in comparison with supportive care alone (Schneck et al 2008).

Another prospective open trial of 34 patients also found that the use of IVIg was not associated with either a significant reduction in mortality or measurable effect on progressive epidermal detachment or on the speed of reepidermalisation (Bachot et al. 2003).

An analysis of nine studies including 156 patients treated with high dose IVIg found that although the mortality rate observed in patients treated with IVIg was 27% versus an expected rate of 30%, it was not possible to make more detailed statistical analyses due to the high diversity in study designs and doses of IVIg used (Faye and Roujeau 2005).

Recently, a larger pooled analysis of 439 patients also found that neither corticosteroids nor IVIg resulted in a significant reduction in observed mortality when compared to mortality predicted by the severity of illness in TEN (SCORTEN) score. (See 2.1.7) (Roujeau and Bastuji-Garin 2011).

It is important to note however, that data from randomised controlled trials is lacking, and therefore many of these findings are inconclusive. The mainstay of treatment, therefore, remains supportive only.

2.1.7 Prognosis

The mortality rate of SJS is estimated to be around 1-5%, and 10-15% in SJS-TEN overlap syndrome. TEN, which affects a larger body surface area, has a higher mortality rate of 30-40% (Bastuji-Garin 1993; French 2006; Breathnach 2010).

The mortality in the elderly has been reported to be almost twice as high when compared with younger adults (51% compared with 25%). This however may be explained by the fact that those who develop TEN which we know is associated with a higher mortality, are likely to be older (average age 63 years) compared to those who develop SJS (average age 25 years) (Schopf et al 1991).

Death usually results from sepsis or multiorgan failure. A severity of illness score for TEN (SCORTEN) has been developed and validated, and accurately predicts mortality from TEN. The scoring system combines seven independent risk factors for mortality: age above 40 years, malignancy, tachycardia above 120 per minute, initial percentage of epidermal detachment above 10%, serum urea above 14 mmol per litre, and bicarbonate below 20 mmol per litre. A score of 1 is assigned for each positive parameter, and the higher the score, the greater the risk of mortality. The authors of SCORTEN showed that the mortality rate was 3.2%, 12.1%, 35.3%, 58.3%, and 90% for scores of 0–1, 2, 3, 4, and greater than or equal to 5 respectively (Bastuji-Garin et al. 2000).

A long-term follow-up study of 64 patients with TEN showed that 28% did not survive the acute episode, and another 23% died following discharge from hospital; the remaining long-

term survivors continued to suffer from ocular (54%) and skin (81%) problems (Oplatek et al 2006).

2.1.8 Long-term sequelae

As described above, sequelae are common in those who survive the acute presentation of SJS and TEN. Cutaneous sequelae include hyper- and hypopigmentation of skin (62.5%), nail dystrophies (37.5%) and loss of the nails. Hypertrophic scarring occurs less frequently, as unlike in full thickness burns, the epidermal appendages (intradermal structures important as a source of epithelial cells, which accomplish reepithelialization should the overlying epidermis be removed or destroyed) remain largely intact, which can allow re-epithelialisation without scarring. Re-epithelialisation of the epidermis begins about 1 week after the ADR and can take up to 3 weeks (Harr and French 2010, Gerull 2011).
Ocular complications are very common and occur in up to 74% of adult survivors and 30% of child survivors. Complications include severe dry eyes (46%), symblepharon (14%), trichiasis (ingrowing eyelashes) (16%), entropion (inward turning of the eyelid) (5%) and visual loss (5%). Photophobia may also occur and may resolve gradually over months (Fellahi et al. 2011;Gueudry et al. 2009;Oplatek et al. 2006)

Mucosal sequelae involve mainly the oral and oesophageal mucosa and to a lesser extent, lung and genital mucosa. Involvement of the gastrointestinal tract may lead to stenosis or strictures and long-term complications such as dysphagia and ileus-like symptoms. Vulvo-vaginal involvement may also lead to vaginal stenosis or strictures. Studies have shown that although vulvo-vaginal complications may be frequent in women developing TEN, only a small proportion of women have symptomatic sequelae such as difficulty with

normal sexual intercourse. Such patients would require surgery to rectify the problem (Meneux et al. 1998;Wilson and Malinak 1988). Although there is limited evidence in the literature regarding the effects of SJS and TEN on long-term fertility, vaginal adhesions and stenosis can result in complications during childbirth (Hart et al. 2002;Kratzert et al. 1988; Oplatek et al 2006).

Unsurprisingly, patients who have survived SJS and TEN have also been shown to experience substantial loss of quality of life after the event. The RegisSCAR study undertaken in Austria, France, Germany, Israel, Italy, and the Netherlands between 2003 and 2005 assessed quality of life in patients surviving SJS and TEN one year after disease onset. This was done using the Short Form (SF)-36 questionnaire, which measures eight domains of health: physical functioning; role limitations due to physical problems; social functioning; bodily pain; general mental health; role limitations due to emotional problems; and vitality. The total score from the questionnaire ranges from 0-100, with lower scores equating to poorer health status, and a score of 100 representing the best health state. Findings from the study showed that SF-36 scores were significantly lower in patients previously experiencing SJS or TEN compared to the general population of the same age and gender (Dunant et al. 2008).

2.1.9 Rationale for current study

We have seen how SJS and TEN have a marked impact on patient morbidity and mortality. It is therefore somewhat surprising that despite this, the experiences, views, and perceptions of patients who have suffered the effects of serious ADRs such as SJS and TEN have not been

previously explored. In my current study, I therefore explored the experiences of adult survivors of drug-induced SJS and TEN, their understanding of the condition, and whether or not these may have influenced their current attitudes towards medicines and ADRs. I also aimed to generate hypotheses regarding their experiences and perceptions, and to develop a theoretical framework which might be used to understand serious ADRs in general. This is a novel area of research, and at the time the study was undertaken, the first detailed qualitative study of patients' experiences and views after suffering any serious ADR.

2.2 Aims

1. To identify and interview adult survivors of drug-induced SJS and TEN, and undertake a retrospective analysis of their experiences of the ADR.

2. To explore survivors' understanding of the ADR.

3. To explore the current views and attitudes of survivors towards medicines and ADRs in general.

5. To generate hypotheses regarding patient experiences and perceptions of SJS and TEN, using qualitative methodology derived from 'grounded theory'

6. To develop a theoretical framework for understanding patient experiences and perceptions of serious ADRs.

2.3 Methods

2.3.1 Qualitative research methodology

I employed a qualitative methodology informed by grounded theory (Strauss and Corbin 1990) to explore the experiences of adult survivors of drug-induced SJS and TEN, which is briefly outlined below.

Grounded theory

Grounded theory methods emerged from collaboration between sociologists Barney G Glaser and Anselm L Strauss, whilst they studied the process of dying in hospitals. As they constructed their analyses, they developed systematic methodological strategies that social scientists could adopt for studying other topics (Strauss & Corbin 1990).

These methods consist of systematic, yet flexible guidelines for collecting and analysing qualitative data (i.e. data which is not numeric in nature) regarding social phenomena to construct theories 'grounded' in the data themselves. Qualitative data can be collected from in-depth interview (which is the focus of the current study), written or electronic documents (the focus of a further study outlined Chapter 3), or directly observed phenomena. Sampling is aimed towards theory construction rather than for population representativeness. Data is analysed early and categorised through a process of 'coding'. Coding refers to attaching labels (or codes) to segments of data that depict what each segment is about. Preliminary analytical notes called 'memos' can be made about emerging codes, ideas related to them, and gaps in the data identified. Through studying and comparing coded data and writing memos, data is interpreted as analytical categories or themes. Relationships are drawn

between different themes, which provide a conceptual handle on the studied experience. An important component of grounded theory research, is the simultaneous involvement in data collection and analysis. Additional data is subsequently gathered to answer any questions that arise, gaps that are apparent in our data, and to check and refine the emerging themes. Data collection may be terminated when 'theoretical saturation' is reached. This is defined as the point reached when no new or relevant data appear to emerge regarding a category or theme, and the relationships between categories are well established (Strauss & Corbin 1990).

The research undertaken, then culminates in a 'grounded theory', or an abstract theoretical understanding of the studied experience (Charmaz 2006).

2.3.2 Rationale for qualitative methodology

There are a number of reasons why a qualitative approach was chosen. Firstly, my study is an exploratory one, in that my aim was to explore experiences, beliefs, views, and attitudes. Qualitative methods can provide a deeper and more detailed understanding of such phenomena, which cannot be easily or effectively done through quantitative methods.

Secondly, I aimed to generate new hypotheses regarding patients' experiences rather than test them, or to draw representative conclusions from data analysed. A qualitative approach was therefore deemed most appropriate.

Thirdly, SJS and TEN are not only very rare, but have a high mortality rate; there are hence only a small number of survivors. Undertaking a quantitative analysis would therefore be

technically difficult due to small sample sizes. Qualitative research however, can be undertaken with even very small sample sizes.

Finally, qualitative approaches are useful for investigating phenomena about which little is known (Strauss & Corbin 1990). As this is a novel area of research and little is currently known regarding patient experiences of serious ADRs, using a qualitative approach would be an ideal method of choice.

2.3.3 Ethical approval

Ethical approval for the study was obtained from the West Midlands Research Ethics Committee, and the Research and Development departments at University Hospitals Birmingham and Sandwell and West Birmingham NHS Trusts. Sponsorship was provided by the University of Birmingham.

2.3.4 Sample selection and recruitment

I aimed to identify survivors of SJS and TEN, aged 18 years and over, admitted over a ten-year period (1998–2008) to one of two Birmingham teaching hospitals. The first hospital, (Selly Oak Hospital or 'SOH', University Hospitals Birmingham NHS Trust), contained a specialist burns unit. A number of patients were therefore transferred here from other hospitals in the UK.

The second hospital (City Hospital, Sandwell and West Birmingham NHS Trust) was a district general hospital, and although had a large dermatology centre and a critical care unit, lacked specialist burns unit facilities.

As SJS and TEN are very rare and are associated with a high mortality rate, purposive sampling of survivors of SJS and TEN which may have allowed an analysis of possible varied perspectives and deviant case analysis was not feasible.

Inclusion criteria

Only adult survivors aged 18−90 years, who had been admitted to one of two hospitals over a 10-year period with a clinical or biopsy confirmed diagnosis of drug-induced SJS or TEN, and who gave full informed consent, were included in the study.

Exclusion criteria

Patients were excluded if they did not have a clinical or biopsy confirmed diagnosis of drug-induced SJS or TEN, had no recollection of having had the condition, had significant communication or comprehension difficulties, were unable to speak English, or who were not able to give their consent to the study for any other reason.

Identification of study patients

Patients were identified either from an existing dermatology research database of fourteen patients who had survived drug-induced TEN at Selly Oak Hospital and had been under the care of a Consultant Dermatologist co-researcher (HL), or from the clinical coding department, through the diagnostic codes 'Stevens-Johnson syndrome' and 'Toxic epidermal necrolysis/Lyell syndrome' (International Disease Classification codes L51.1 and L51.2 respectively) assigned to them when they were admitted to either Selly Oak or City hospital.

As it was likely that the majority of patients identified would not have been under the direct clinical care of the research team, ethical approval could only be obtained to contact these patients by letter to invite them to participate in the study. Ethical constraints prohibited accessing the medical notes of these patients to confirm the clinical diagnosis prior to gaining explicit patient consent. This was therefore only done after patients had agreed to participate in the study, and gave explicit consent to the researcher to access their medical notes.

In total, 89 patients with the described diagnostic codes were identified (Fourteen patients from the pre-existing database, and 75 patients from the clinical coding department). Forty-one of these were immediately excluded as they were either identified as deceased, their contact details were missing, or they were currently under the age of 18 years, and hence did not meet inclusion criteria for the study (See figure 2-1).

Patients invited to participate

The 48 remaining patients were contacted by letter (See Appendix A) to explain the purpose of the study and inviting them to take part. A study information sheet (Appendix C) was also enclosed with the letter as well as a reply slip which they were invited to complete and return in a pre-paid envelope, to indicate whether or not they wished to participate in the study (Appendix B). They were also invited to contact the researcher via email or telephone to indicate their wishes, or if they had any queries about the study.

Patients agreeing to participate

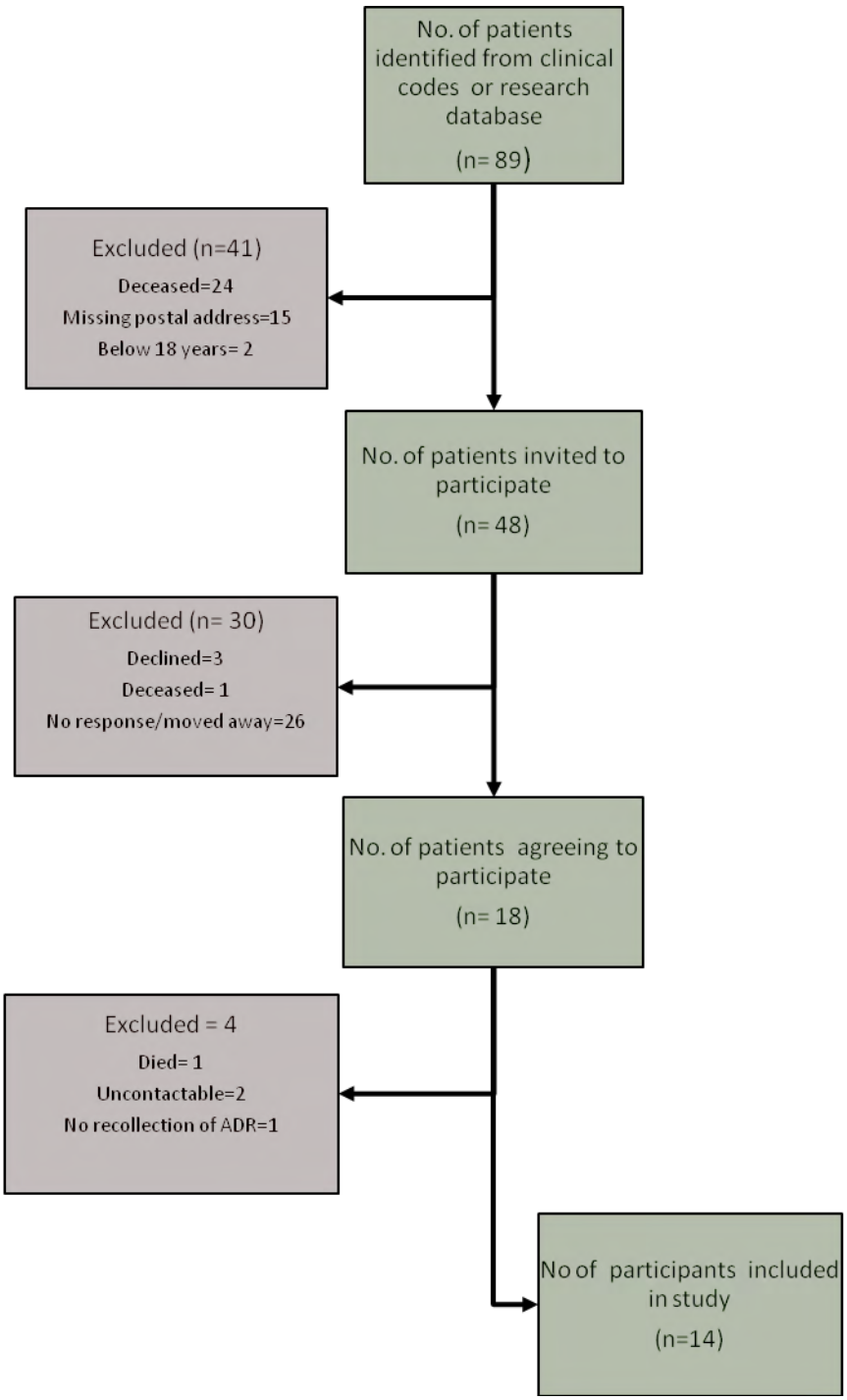
Eighteen patients agreed to participate in the study. Of these, four were excluded: one died from an unrelated condition, two were subsequently uncontactable, and one patient had no

recollection of being diagnosed or admitted to hospital with the condition. All fourteen remaining patients fulfilled the inclusion criteria for the study. As my research focused on patients' own perceptions and beliefs regarding their experience of the ADR rather than the health care provider's perspective or 'version of events', medical records and notes of consenting participants were only checked to confirm the diagnosis of drug-induced SJS and TEN.

Non-responders and declining patients

Twenty-six patients did not respond to the initial invitation to participate. The researchers were contacted in one case and informed that the patient was no longer living at that address, and hence hadn't responded. We were unable to confirm whether or not any of the remaining non-responders had similarly moved away, or had died since their admission to hospital. Two patients formally declined. Of those who either declined or did not respond, 18 (64%) were female and 10 were male, and the age range was 20−89 years (mean age of 46.8 years).

Figure 2-1: Identification and recruitment of study patients



Arrangements to attend for interview

The fourteen survivors included in the study were contacted by telephone and invited to attend for an interview either at the hospital, at home, or at a venue of their choice, according to patient preference.

Participants were offered reimbursement for travel or parking expenses, but no other financial incentive was offered for taking part. On attendance at interview, and after ensuring that the information sheet had been read and understood, the participant was invited to sign a consent form for the study (Appendix D). Participants were invited to ask any questions they had regarding the study prior to signing the consent form. It was also explained that should they change their mind, they could decline to be interviewed at any point, up to and including during the interview. Participants were then assigned a unique reference number to ensure anonymity, and all subsequent interview recordings and transcripts were labelled with this code. Names or other personal identifiers were not recorded anywhere in the researcher's data.

2.3.5 Ethical considerations

Qualitative research aims at an in-depth understanding of an issue, including an exploration of participants' experiences and beliefs. Although talking about even traumatic experiences can be psychologically beneficial for those doing so (Lyubomirsky et al. 2006), some individuals may find talking about their experiences potentially upsetting or anxiety provoking. The potential for this was explained to participants, and they were told that they

could stop the interview at any time and withdraw from the study if they felt unable to continue.

Both researchers (ARC and I), involved in conducting the interviews have clinical backgrounds and were experienced in dealing with patients who may have experienced serious or distressing illnesses. We both therefore planned to remain vigilant for any potential participant anxiety arising during the interview process, and provide support and reassurance to participants at all times. Furthermore, contact details for a counselling service were to be made available if participants wished to talk through any anxieties with a trained counsellor.

Another potential concern, related to the possibility that participants may not be aware that a drug was thought to have been responsible for the condition with which they were admitted to hospital. As the researchers conducting the interviews were not involved in the direct clinical care of the patient, it was decided prior to commencing the study, that it would be unethical to inform the patient of this if they were unaware.

The letter sent inviting patients to participate in the study, therefore mentioned their admission to hospital with a 'skin condition' but did not mention either SJS or TEN by name or the suspected causes. We also ensured that questions related to a drug cause were only asked if participants volunteered this information when asked what they were told or what they believed the cause to be.

2.3.6 Data collection

Semi-structured interviews of all fourteen patients were undertaken using a standardised interview topic guide devised by myself (TFB), with revisions made by ARC, and REF. (See Appendix E).

Patients were interviewed independently by TFB (10) and ARC (four). All interviews were audio recorded with the patient's permission, and the researcher also made accompanying written notes where required, for example, to document non-verbal responses from the patient during the interview, such as smiling, looking surprised, appearing upset, etc.

Closed questions were initially asked to confirm basic demographic data including age, date of birth, and ethnicity. Following the standardised interview topic guide, open questions were asked regarding their experiences of the condition and the circumstances surrounding it, the information they were given at the time of the event, their knowledge and understanding of the ADR, their beliefs regarding the cause or precipitant of the adverse event, the impact of the ADR on their current lives, their views towards the culprit drug (if they believed a drug caused the reaction), and the safety of medicines in general. Patients were encouraged to openly express their own views with minimal intervention from the interviewer. The interview topic guide evolved as interviews progressed, and a final version was developed after the fifth interview.

The role of 'reflexivity' during data collection and analysis was also considered. The process of reflexivity refers to the influence of the researcher's own position, emotions, views, and

responses, which may be conveyed to participants, and which in turn, may result in participants continually adjusting their responses as the interview continues. This of course, may be a potential source of bias, and was taken into consideration by the researchers by reflecting on the impact of their presence, position, and emotions on participants' responses, and reflecting on the impact of their own views on the way they interpreted and analysed the data (Corbin and Strauss 2008).

At the end of the interview process, participants were thanked for taking part in the study, and invited to listen to the audio-recording if they wished. They were also encouraged to contact researchers in the future if they had any further questions or queries.

2.3.7 Analysis

Audio recordings of interviews were transcribed verbatim, without any amendments for grammar or otherwise into standard Microsoft Word 2007® documents, and labelled with participants' unique reference codes.

These were then imported into the qualitative software package NVivo 8.0 (QSR International) which was used to manage the coding of text within transcripts, and for organising passages from text into themes and subthemes.

Text was then analysed using an approach based on grounded theory(Strauss & Corbin 1990). Transcripts of interviews were analysed in five steps: (i) identification of themes; (ii) generation of codes to label passages; (iii) revision of themes and coding scheme in light of

newly accumulated data; (iv) application of codes to the final data set; and (iv) exploration of the relationship of various themes amongst patients. Data analysis was undertaken as the interviews progressed, ensuring that emergent themes were analysed as they arose.

All interview transcripts were independently analysed and initial coding schemes independently generated by TFB and ARC; any variations in coding were resolved by discussion to achieve consensus. A third researcher, REF, also analysed the emerging coding framework to ensure rigour in the analysis. TFB elaborated the final coding scheme, and consistency was confirmed through blind dual coding with ARC of five transcripts. After 12 interviews, analysis showed that we had reached theoretical saturation, defined as the point when no new themes, concepts or relevant data regarding a category emerge (Strauss & Corbin 1990).

2.4 Results

2.4.1 Descriptive analysis

Fourteen adult survivors were interviewed, of whom eight (57%) were women. The age range of participants was 21–82 years, with a mean age of 57 years. The majority of participants (11/14) described themselves as White British, two as Asian British (Indian origin) and one as Black British (Caribbean).

The majority of participants (10/14) had been admitted to the SOH Burns Unit (five of whom were initially admitted to a general hospital elsewhere in the UK), and the remainder four patients to City Hospital, Birmingham. Six participants had been diagnosed with drug-induced SJS, and eight with drug-induced TEN, as confirmed from medical notes and by participants themselves.

During questioning, all patients were aware that that the reaction was drug-related, with the majority of cases being due to antibiotics including penicillins and cephalosporins (9/14), in keeping with previous epidemiological studies (Roujeau et al 1995). Three cases were attributed to anti-epileptics (phenytoin and lamotrigine), and the remaining two cases to allopurinol and sulfasalazine. These drugs were prescribed by healthcare professionals for a variety of indications (See Table 2-2).

Table 2-2: Suspected culprit drugs and their indications as described by patients

Patient ref no	Age (years)	Gender	Diagnosis	Culprit drug	Indication
P1	75	Female	SJS	Amoxicillin,trimethoprim or Septrin (cotrimoxazole)	Urinary tract infection
P2	44	Female	TEN	Lamotrigine	Epilepsy (New diagnosis)
P3	65	Male	SJS	Antibiotic (unsure which one)	Pneumonia and empyema
P4	70	Female	TEN	Cefalexin	Respiratory tract infection
P5	27	Female	SJS	Flucloxacillin or Ibuprofen	Cellulitis (foot)
P6	66	Female	TEN	Cephalosporin	Pre-operative prophylaxis (hip replacement)
P7	21	Male	SJS	Erythromycin	Tonsillitis
P8	82	Male	TEN	Allopurinol	Gout
P9	65	Female	TEN	Phenytoin	Seizure prophylaxis post surgery (brain tumour resection)
P10	74	Male	TEN	Trimethoprim	Urinary tract infection
P11	65	Female	TEN	Sulfasalazine	Rheumatoid arthritis
P12	54	Male	TEN	Phenytoin	Epilepsy secondary to brain tumour
P13	41	Male	SJS	Penicillin	Lower respiratory tract infection
P14	48	Female	SJS	Cefaclor	Lower respiratory tract infection

2.4.2 Qualitative analysis

Qualitative data were classified into seven main themes: survivors' experiences of the condition, their understanding of SJS and TEN; their interpretation of why the ADR occurred; the impact that the ADR has had on their current life, including their views towards the safety of medicines; views on medicines information sources; views on patient reporting of ADRs; and their current views on events leading to the reaction with 'hindsight'. A number of subthemes were also identified, and the resultant taxonomy is outlined in Table 2-3.

Table 2-3: Themes and subthemes identified through interviews with survivors

<table>
<tr>
<td>Experiences of SJS/TEN

• Circumstances leading to ADR
• Symptoms and initial presentation
• 'Confused for another condition'
• Reaction of prescribing doctor
• Support and communication
• Healthcare professionals' awareness of SJS/TEN</td>
<td>Understanding of SJS/TEN

Awareness of:
• Drug cause
• Name of condition
• Rarity
• Seriousness and potentially fatal
• Spectrum of disease
• Treatment limitations</td>
<td>'Why the ADR occurred'

• Ignoring existing allergies
• 'Too high a dose' of the drug
• Failure to monitor blood tests
• Culprit drug unnecessary
• Chance/ 'A fluke'</td>
</tr>
<tr>
<td rowspan="2">Impact of ADR on current life

• Fear of/ avoidance of medicines
• Views towards culprit drug
• Views on safety of medicines in general
• Irrational fears
• Trust in healthcare professionals
• Precautions
• Long term physical and psychological effects (e.g. scarring)</td>
<td>Views on information sources regarding ADRs

• Internet sources
• Patient information leaflets
• Healthcare professionals</td>
<td rowspan="2">Hindsight

• Views on warning prior to the event</td>
</tr>
<tr>
<td>Views on patient reporting of ADRs</td>
</tr>
</table>

2.4.2.1 Experiences of SJS/TEN

Circumstances leading to ADR

Survivors had a good recollection of events and described a variety of circumstances which led to them developing SJS or TEN resulting in hospital admission.

The majority of survivors described the event occurring in the community after being prescribed the culprit drug by health professionals, with a few cases occurred in a secondary care setting after being admitted to hospital with a different complaint.

Some described being prescribed the culprit drug for illnesses which were serious in themselves if left untreated (e.g. phenytoin for seizures secondary to a brain tumour or serious infections) as can be seen by the interview extracts below:

> ***P3 (65-year-old male)*: "**I went into hospital in August with pneumonia. Then a lung abcess. I've got emphysema and COPD [chronic obstructive pulmonary disease], so my lungs wouldn't stand an operation for the abscess so the only hope I'd got was a course of antibiotics...and after three days I started to come up in blisters and swell up like the Michelin tyre man... At this stage I couldn't eat or drink properly because of the ulcers in my mouth, the blisters in my mouth."

> ***P12 (54-year-old male)*:** "My wife tells me that we were heading up to Shrewsbury, and I started, I don't remember this, but apparently I started acting out of character, and I started fiddling with the dashboard, and the next minute, I'm slumped. And I'd lost consciousness, and basically had a blackout for 5 minutes...I then had further scans at the Queen Elizabeth Hospital, and one of the consultants came in…he just walked in and said actually you've got a brain tumour...I was roughly a week in Queen Elizabeth Hospital, I was then prescribed a number of drugs, and one of them was the dreaded anticonvulsant Phenytoin…that was the little horror which I later found out…"

***P2 (44 year old female)*:** "How it all started, it was the year 2000 I just finished work, I collapsed at the top of the landing, and the children were only small.. I'd never had an epileptic fit before, and so he [P2's husband] didn't know what it was, and he called an ambulance, they assured him that it was an epileptic fit…and they admitted me to the Manor, and they started me on some epileptic tablets which was called Lamotrigine...and the tenth day, all my eyes swelled and my lips…but on the leaflet it did say you could have a mild reaction (laughs) like conjunctivitis …it was the weekend…and I rang the emergency doctor and he said you're allergic to the tablets and he advised me to stop taking them."

P14 (48-year-old female): "It was back in 30th November 1993. I remember that day like it was yesterday. I got flu like symptoms and I called the doctor out he came out with "Oh, you've got severe infection," gave me some strong antibiotics, it was Distaclor MR (ceflacor modified release) at the time fairly new on the market and it was 375mg and he says "oh you'll be alright by tomorrow." Within 24 hours my body just started to swell up, mainly my hands and the insides of my feet, passing urine was very painful. So I waited until the morning, I hadn't slept all night and phoned an emergency doctor, one doctor came out and said "I don't know what's wrong with you, but you need to go to the hospital."

Symptoms and initial presentation

Survivors vividly recalled how they first presented with SJS or TEN, and the initial symptoms they experienced. The majority of survivors recalled experiencing 'lip swelling', 'blisters' or 'ulcers' affecting the skin and oral mucous membranes, with extensive 'shedding of their skin' and severe pain as a result:

P2 (44 year old female): "…and the tenth day, all my eyes swelled and my lips...it was like blisters, constant diarrhoea really, and severe pain going to the toilet, and generally in a lot of pain, because it was like my skin coming off my body really."

P3(65-year-old male): "...and after three days I started to come up in blisters and swell up like the Michelin tyre man. Erm, they called the dermatology doctors in, who thought it was er, a chemical reaction. At this stage I couldn't eat or drink properly because of the ulcers in my mouth, the blisters in my mouth. So I was given, I was fed via a tube. I know I was very poorly, because they called for the family. I swole to a terrible size. I looked like I'd been in a fire."

P11(65-year-old female): "I had arthritis... the arthritis in my hands all flared up, wrists and elbows, shoulders, all badly and then I went to my GP and he gave me a course of tablets, ibuprofen, which didn't do anything, so he said I'll send you to the hospital. They sent me to the hospital, and they said I would need some tablets. They gave me sulphasalazine, which I'd never had before... and I was feeling very ill in August, about two weeks after I'd taken the tablets and didn't connect it...And then it got worse, it was all over my face, and then it started... , it was blistered, like, I could see the spots growing up my leg it was going through the blood stream obviously, and it got worse... it was burns by this time, it then started to blister and of course bleed..."

Confused for another condition

Others recalled that their signs and symptoms were initially confused for other conditions including chicken pox, oral thrush, *Herpes simplex* infections, and viral upper respiratory tract infections, both by themselves, and healthcare professionals:

P1 (75-year-old female): "My own GP hadn't experienced anything like it you see, so when this rash had come, I think he did think it was chicken pox, so I took another 2 more [tablets]…it was all in me system...it got out of hand then..."

P2 (44 year old female): "...and I rang the emergency doctor and he said you're allergic to the tablets and he advised me to stop taking them...But then the next day, I couldn't get out of bed, it was like flu type symptoms, and this rash was developing then, so my husband called the GP, and he thought it was chicken pox! So he advised me to take another tablet, which I did..."

P11(65-year-old female): **"**He said "it could be a number of things, I don't know what it is and you need to get there [hospital] quick" and when I got in, initially they were looking at glandular fever and they asked if I'd been out of the country, which I hadn't. Other than taking that medication and pain killers, I hadn't taken anything else."

P2 also recalled how her general practitioner (GP) expressed feelings of shock and regret after the correct diagnosis was made:

> ***P2 (44 year old female):*** "Well, um I was surprised with my own GP, because it must have been something so rare, because my own GP came to the Manor [hospital]."
>
> ***Interviewer:*** To have a look at you?
>
> ***P2 (44 year old female):*** "Yes (laughs) he was apologising…..I think he was quite shocked really….and he did come out after to see me quite a lot, a lot of home visits!"

Healthcare professionals' awareness of SJS/TEN

Several expressed surprise at the perceived lack of awareness of SJS and TEN amongst healthcare professionals as can be seen from the extract below:

> ***P1 (75 year old female):***"Well, I'd never heard of it, and when the doctors themselves didn't know anything about it, it was all a bit scary…"
>
> ***Interviewer:*** "Do you find it surprising that some people [doctors] didn't know what it was?"
>
> ***P1 (75 year old female):*** "I am surprised about it, because as I say, I'm not the only one and if they [the doctors] don't know, how do they get on?"

Perceived reaction of prescribing doctor

One survivor with a known penicillin allergy, who developed TEN after being prescribed a cephalosporin, describes how she perceived the prescriber as anxious and 'defensive' about the event, but described how she was provided with detailed information to highlight the rarity of the ADR:

> ***P6 (66-year-old female):*** "I did make a point of saying to Dr D I am allergic to penicillin when he came to do the pre-op visit I don't think he took sufficient notice of that, he has investigated cephalosporin before and I think it's 3rd generation cephalosporin now and I think there is only a 1% link between that [and penicillin], he has investigated this and he was very keen to give me all of the statistics when I went to my follow up visit, I think he thought I was going to sue them or something, they were all very protective... the anaesthetist was particularly anxious because it's a litigious society isn't it, He should have taken more care and it might not have been that I don't know."

Support and communication during event

Most patients felt well supported both by their GPs, and in particular, by the healthcare staff caring for them during their admission.

The majority of survivors (11/14) were seriously ill with the condition, and around half spent time on an intensive care unit after admission to hospital. Although the majority described being directly admitted to one of the two Birmingham hospitals included in the study, a few had initially been admitted with the ADR to another hospital in the United Kingdom, and had subsequently been transferred to the SOH Burns centre in Birmingham for further management, as can be seen in the extracts below:

> ***P11 (65-year-old female):*** "...And then it got worse, it was all over my face, and then it [SJS] started...Burton haven't got the facilities to keep me, because it was burns by this time, it then started to blister and of course bleed, and I was sent to Selly Oak just about a week after I'd been in Burton, and from then on Selly Oak, they of course, treated me, and that is sort of… what six weeks there I think."

> ***P4 (70-year-old female):*** "Then they must have contacted the burns unit at Selly Oak Hospital, it was either that, or Chelmsford, or somewhere in London or Bristol…..and we opted for Selly Oak Hospital, just up the motorway, more convenient! They were going to send me by helicopter but the doctor said I was too poorly, the vibration was not going to be good for me, so they sent me in an ambulance …I was fairly unconscious when I arrived..."

Many recalled positive experiences of the medical and nursing care they received and felt that they were given adequate information about the condition, treatment, and prognosis. Survivors fully appreciated the risk the ADR had posed to their lives at the time and expressed gratitude for the health professionals who treated them, as can be seen from the extract below:

> ***P12 (54-year-old male)*:** "The nurses were wonderful, all the care staff, I mean Selly Oak, we knew they were the best... (Pauses and becomes tearful)…God…it was touching! (Laughs). Oh I'm welling up! (Laughs). They saved me, they saved me..."

Survivors who were managed in the specialist Burns Unit, felt better supported and managed than those who were not. This was even true when it was made clear to them that treatments available were supportive only, as can be seen from the extract below:

> ***P3 (65-year-old male)*:** "Yes, I re-illustrate that fact that all the people from the dermatology department [SOH] have all been to good bedside manners school, absolutely charming, very supportive, very informative... I knew, they told me what I needed to know at the time...I'll sing the praises of the dermatologists...they were very good, they came out of their way to see me; although they virtually made it clear that there was nothing they could do for me when I was in, at the crisis point."

Those managed in non-specialist centres however, describe feeling under-supported, primarily, they believed, because the hospital lacked the staffing, facilities and experience to care for them, as can be seen in the extracts below:

> ***P14 (48-year-old female)***: "My family were with me 24/7, there was somebody with me 24/7 because, I aint blaming the staffing, but I know that if I needed something I needed it, especially when it came to water because I could literally feel my lips drying out by the millisecond ...and they weren't able to provide me with that one to one care, so my family were always with me and I don't think how I would have made it if I had to rely on the hospital staff to be caring for me I wouldn't have made it."

Interviewer: So would you describe your experiences predominately positive or predominately negative?

***P14 (48-year-old female)*:** "They did what they could and I understand the restraints they are under. If you take the understanding out it was poor... I understood why they couldn't do what they needed to do...and it's like with my feet when they had to lance my feet, my sister in law did it, because of having to wait around for somebody to be free, because I was on a chronic ward."

Interviewer: What happened when you got to H*****? [District general hospital where P12 was initially admitted]

***P12 (54-year-old male)*:** "Well they tried their best (smiles sadly, and sighs), I think they…were out of their depth...[I'm] less complimentary about to be honest, I mean they were very good, but the doctors….I don't know…I was obviously given various creams, but perhaps wrong ones, um, and I was there into day 4...my skin I noticed was beginning to um, like ulcerate and blister...and I mentioned this to one of the nurses and she looked in horror and said oh my life, what's this?…"

The husband of one survivor, initially managed in a non-specialist centre, contacted the manufacturer of the implicated drug directly for more information, as he felt he lacked information at the time of the event.

Husband of P4: *"*I must have been told [that it was TEN] at the same time [as P4] because I looked it up on the internet, and was most alarmed by what I read…and then I got onto Dublin where this batch was made, I don't know how I found that out, they wouldn't talk to me because I wasn't a medic, um, I was screaming up and down...I said have you met this before, we wanted help….I remember thinking, I can't think why I'm doing this, why isn't someone else finding out more…"

Another survivor felt that that the healthcare professionals caring for her could have communicated better, and that she was not allowed to be involved sufficiently in decisions regarding her care. She also felt that the staff were 'overwhelmed' by the severity of her condition, and that although they could do little to treat it, they were not honest and open with her about this. These perceptions have damaged the trust and confidence that she now has in the healthcare system many years later:

> ***P14 (48 year old female):*** "I did not have any answers whatsoever. Nobody would give me an answer. 'Oh I'll get back to you on that one.' And I didn't have any answers, and yeah, thinking about now, after I'd got through, they didn't know, and they didn't want to admit to not knowing, but I would have had more faith them if they would admit it…I was asking 101 questions, it would have been nice for them to say 'look, I don't know', but they wouldn't."

Regardless of where they were managed, the majority of survivors and their families relied heavily on internet sources for more information at the time of the event, with a few contacting patient support groups set up for sufferers of SJS and TEN as can be seen from the extract below:

> ***Interviewer:*** What did they [the hospital] tell you about the condition?
>
> ***P12 (54-year-old male)*****:** "Not a great deal, not a great deal. K*** (P12's partner) started looking at both [SJS and TEN] on various websites and she told me that it scared the living daylights out of her, and she's a pretty strong woman when it comes to anything medical, and she said she had to go off the website…"
>
> ***P1 (75-year-old female)*****:** "... if my brother in law hadn't go in touch with America [American SJS support group website], I wouldn't have known what it was…and you've got something there in black and white that you can read, which brings it home to you…"
>
> ***P13 (41-year-old male):*** "...the doctors never really told my family the risks, it was 'he has Steven Johnson syndrome, it's a rare condition' and that's where the bells rang and my sister went on the

internet and looked it up, and told people, the doctors don't actually tell you the true risk side of things, they keep it back because they don't want to scare anyone."

2.4.2.2 Understanding of SJS and TEN

Survivors had a good knowledge and understanding of the condition. All were aware that their condition was drug-related, and all but one knew the specific drug implicated. Most (11/14) survivors knew that the ADR was very rare; they recall either being told this directly by healthcare professionals caring for them at the time of the event, or deducing this from the fact that they were treated as a 'novelty' while in hospital:

***Interviewer*:** Do you think that this is a common or rare event?

***P3 (65-year-old male)*:** "I would imagine it's quite rare as so far as erm, I know it's a teaching hospital so people have got to educate this many people as they can, but it is pretty rare from the reaction I was getting from the medical staff a lot of them haven't seen it before...And it was evident that a lot of the nursing.. people at the hospital hadn't heard of it, because quite a few people came to have a goggle at me, and see what was entailed with this..."

Most were also aware that it was potentially fatal (13/14) and that treatments were limited and largely conservative. Survivors and their relatives however, expressed surprise at the seriousness of the reaction. Before the ADR occurred, they were not aware that such serious reactions could occur as a result of taking medications, and this is illustrated by the comments made by P7 below:

P7 (21 year old male): "I didn't know people could be ill like that. Being fourteen, I didn't know that…well fourteen to fifteen, I just didn't … (Long pause)"

Interviewer: "You didn't think it could happen to someone like you?"

P7 (21 year old male): "Yeah, I'm just surprised in a way that allergies of that severity could happen."

Some survivors were also aware that a spectrum of disease existed, with a 'milder' form (SJS), and a more serious form [TEN] affecting a greater body surface area:

> ***P12 (54-year-old male)*:** "...but the major difference between the two [conditions] is the area of skin that's affected apparently, with one, it's less than the other, one's more localised isn't it, and the other's more extensive….with me, I don't know, there was two thirds of my body where I'd lost my skin…"

2.4.2.3 Interpretation of why ADR occurred

Survivors held different beliefs regarding why the ADR occurred. Only two survivors believed that the reaction was unavoidable or idiosyncratic, and correctly understood that it could not have been predicted by healthcare professionals, putting it down to 'chance' or 'a fluke' given its rarity, as can be seen from the quote below:

'A fluke'

> ***P8 (82 year old male)**:* "…Allopurinol…, I mean, it's a standard gout cure I understand...but it went the wrong way…I mean I've no worry about the way the GP dealt with it, so it was a perfectly proper thing to do. It's just a fluke that it hits one in a million."

The majority however, believed that the reaction was avoidable. Expressed views of its cause included medical staff ignoring existing allergies (three survivors), being given too high a dose of the drug (three survivors), and failure to monitor blood tests (one survivor):

Ignoring existing allergies

Those with existing allergies felt that this should have alerted the prescriber that they were 'at risk', and the culprit drug should therefore not have been given to them, as illustrated by the quotes below:

> ***P6 (66 year old female)****:* "I have a history of allergy and I have had two very serious reactions, one when I was 29 and the other about 20 years ago and I had warned the hospital that I was allergic to penicillin and anything associated, but it's a bit of a factory there and everybody gets cephalosporin, I don't think anybody really questioned the fact that there was a relationship between cephalosporin and penicillin… I did make a point of saying to Dr D I am allergic to penicillin when he came to do the pre-op visit I don't think he took sufficient notice of that…"

> ***P4 (70 year old female):*** "Well I felt bitter that I should not have been given cefalexin, but it was on my notes it said I'm allergic to penicillin... and there is a train of thought that cefalexin is closely related to penicillin, and she [the GP] shouldn't have given me that knowing my history, all my notes say no penicillin...I feel she [the GP] should have looked it up on the internet, she's got the means, she should have inquired rather than handing out willy nilly…"

Too high a dose or failure to monitor blood tests

Survivors also believed that the ADR could have been avoided if they had been prescribed a lower dose of the culprit drug, or if their GP had 'monitored their blood tests' as can be seen from the quotes below:

> ***P12 (54 year old male):*** "I reckon, it's a dreadful thing to say, I reckon my GP had taken his eye off the ball when it came to my blood tests, maybe the doses I was on was too much for me, maybe something a bit more modest would have been a bit more appropriate for me, I mean who knows…"

> ***P2 (44 year old female):*** "But the epileptic nurse came by, she did say, ooh this seems a high dose for someone who's only had one fit! …my lips was really sore, they was like all gone black, it was like a crust, it was terrible….but um, perhaps if it had been a lower dose, perhaps it might not have happened."

Culprit drug unnecessary

Finally, one survivor believed that the drug prescribed was 'unnecessary' for the condition (tonsillitis) he presented with as it could be treated conservatively, and implied that the reaction could have therefore have been avoided:

> ***P7 (21 year old male)*****:** "That was it; it's the whole 'benefit outweighs the consequences or side effects', so I thought tonsillitis is recoverable, so after that, I thought, no more unnecessary stuff for colds, flus…"

Another survivor also implied that she shouldn't have been prescribed the culprit drug as the condition for which it was prescribed was minor, but didn't directly cite this as a reason for her developing the ADR:

> ***P4 (70-year-old female)*****:** "It was only a cough for heaven's sake! It wasn't anything life threatening for heaven's sake!"

2.4.2.4 Impact of ADR on current life and views towards medicines

The experience of a serious ADR had a profound impact on the current lives of survivors, both physically and psychologically. Their experiences also influenced their views towards taking medicines and their trust in health professionals.

Fear of or avoidance of medicines

Since experiencing the ADR, the majority of survivors were now fearful of or avoided taking medicines altogether. Some also expressed a marked fear of becoming ill enough to necessitate their use, implying that they feared that taking any medicine might lead to a recurrence of or similar adverse event.

One survivor for example, admitted that she avoided going to see her General Practitioner if she had an infection of any kind, to avoid being prescribed antibiotics:

> ***P1 (75 year old female):*** "But the only thing now is, it's made me so scared of taking pills...I won't go to the doctors if I can help it no….um, you know if you got infections or anything like that, I won't go, and if I had to go, was forced to go, he gives me tablets, I ask him…I must be the worst person, the worst nightmare they've had! (Smiles)...I ask him, then I ask the chemist (laughs), then I think, I'm not taking them! Just in case, you know? It's frightening…"

Another survivor who had developed TEN after taking lamotrigine for newly diagnosed epilepsy refused to take any antiepileptics after the reaction for a number of years, as she was too frightened to do so, and suffered from at least two serious epileptic fits as a result. She described how her fear also extended to her children when they were ill and required medicines:

> ***P2 (44 year old female):*** "...what I found that happened when I came out of hospital, if I had a headache or anything, I was too scared to take any tablets, with C**** (Patient 2's son), when he was 3 or 4, if he had a temperature…any other time, I'd just have the Calpol ® [branded paracetamol suspension] , but I keep reading the instructions over and over again, (laughs)...the one particular night, he did have a sickness bug, I felt as though my legs were shaking because I just couldn't cope...I'd read a Calpol® label, not once but half a dozen times! (laughs)… thinking, I hope I'm doing the right thing!"

A few survivors also expressed fears regarding medicated supplements such as 'cough sweets' and certain foods, as illustrated by the quotes below.

> ***P7 (21 year old male):*** "…I stopped taking any medication unnecessarily, like paracetamol, penicillin, Nurofen [branded Ibuprofen], and …Lockets [medicated lozenges], because they're like medicated inside aren't they…and, so I stopped taking all that kind of stuff ...and I get really bad migraines as well, that will actually make me throw up, but I still don't take Nurofen…because of the chance…"
>
> ***P1 (75 year old female):*** "I think it's just made me aware of everything really...um, if er, if new sweets have come on [to the market] or anything ...from different foods, you think, knowing that it's stupid! But it does…you think about it!"
>
> ***Interviewer:*** "So if you're taking or eating new foods, you worry about it?"
>
> ***P1:*** "That's right; it goes through your mind, and I think, God, you're so stupid thinking this, when it's a medicine that's caused it, why should the food cause it? It's just psychological really."

Interestingly, although P7 now avoided all medicines or products he considered related to medicines such as medicated lozenges, he admitted that he still occasionally used recreational drugs such as cocaine and cannabis. When questioned about this, it was apparent that he did not attribute the same risks to these drugs as he did to those used for therapeutic indications.

Views towards culprit drug

Many survivors did not appear to have negative views regarding the safety of the culprit drug in general, despite having had a serious reaction to the drug themselves. They were aware that although taking the culprit drug would be life-threatening for them, this was not necessarily the case for others, including family members. They believed that the reaction was specific to themselves and their individual circumstances:

> ***Interviewer:*** So what are your views on the safety of the drug that caused your reaction, the sulphasalazine?
>
> ***P11 (65-year-old female)*****: "**I don't think it's safe from my point of view, whether anybody has that opinion I don't know, but I definitely … I would never have it again. They told me...Because every case is different really. What suits you, wouldn't suit me. Obviously, this didn't suit me and probably a thousand people have taken it and it hasn't affected them..."

Views on the safety of medicines in general

The majority of survivors indicated that their views on the safety of medicines in general had not changed since the reaction, despite a change in their own medication-taking behaviour. They were aware that all medicines are associated with benefits and harms, and that these had to be taken into account when deciding to take medications. Views on using or prescribing medicines only when they are necessary were also discussed by survivors, including avoiding the over-reliance on or over-use of medicines as shown in the quotes below:

> ***P4 (70 year old female)****:* "Well…in general they're [medicines] a good thing if they are not abused because there are a lot of patients with illnesses who are kept alive thanks to the medication, they've got to be used with common sense not just dished out willy nilly..."

P10 (74 year old male)*:* "I suppose it depends how many [medicines]... if you're taking medicines all the time, but suppose sometimes you've got to take it haven't you? As I said at the beginning you do take that risk but if you're taking it for a reason… like at the time I needed that, so that's why I took it..."

P14 (48 year old female)*:* "They're good as long as you understand the side effects of it. As long as you consciously understand the side effects of them, and again it's down to the individual on whether you want to, I want to...I need to know the worst case scenario so I can make my decision, consciously, because I've got to live with it."

Trust in healthcare professionals

For some, the experience of a life-threatening reaction to a drug prescribed by a healthcare professional had diminished their trust in the advice given to them by such professionals, regarding treatment. A number of survivors, for example, described having less trust, or 'blind faith' in what they were told by healthcare professionals since the reaction; this was particularly true of those who believed the reaction could have been avoided if the healthcare professional prescribing the drug had acted differently:

P1 (75 year old female): "... the only thing I feel is, you're scared… well I am, of going to the doctors, and he tells me you've nothing to worry about, and all this and that, but I'm still nervous of taking anything... he gives me antibiotics and he says you 'should' be alright with it, you should, but I said to him, I can't depend on his 'you should', I've got to be certain, if I'm not sure, I just won't take them."

P3 (65 year old male): "...you see that the public have got a blind faith in the medical world and I'm not so blind now, I'm more challenging..."

P14 (48-year-old female): "I'm reading and since that happened and any medication I take, I'm reading everything before I'm taking it. Whereas previously, previously I was of the school of thought I use to think 'oh the doctor knows what he's talking about. Now I'm going, 'they ain't got a clue, they can't be...' and that's the impression it's left on me."

Physical and psychological sequelae

The main long-term physical complication was cutaneous scarring, affecting survivors both physically and psychologically. Survivors discussed how scarring after the event had, for example, made them less confident, and reminded them of their traumatic experience:

> ***Interviewer:*** You mention your skin will never be the same. Has that changed the way you have to behave or live your life?
>
> ***P11 (65-year-old female):*** "Yes, apart from what I wear, I've got to sort of think, I can stand that...sleeves, I [have to] keep wearing. My legs are a mess; I don't want to wear..." (Struggles to speak, becomes tearful).

One survivor also appeared to exhibit symptoms of post traumatic stress disorder:

> ***Interviewer****:* Do you think it has affected your life psychologically at all?
>
> ***P13 (41 year old male)****:* "Yes...being depressed, yes, because as I said I get flashbacks, your memory goes but you remember certain things like when I'm having a shower or taking my top off or look in the mirror it all comes back again".
>
> ***Interviewer****:* You remember the events again?
>
> ***P13 (41-year-old male)***: "Yes because I'm scarred in my mind as well as scarred on my body...I have flashbacks to my illness ...the doctors were great and the hospital was great…but what let me down was the aftercare because ok, I got home and had to go back for checkups, but I said what about my scars? And the doctor was great he said you're a big strong lad, you'll be able to cope, but really I don't."

Only one survivor (P8) developed long-term ocular sequelae requiring numerous surgical procedures, and which resulted in significant visual impairment.

2.4.2.5 Views on patient reporting of ADRs

Only one survivor (and her husband) was aware that ADRs could be directly reported by patients to the Medicines and Health Care products Regulatory Authority (MHRA):

> ***Husband of P4:*** *"*Somehow I got onto the [organisation of] risk management of medicines….I got a letter here from them, and of course I sent in a yellow card… (Shows interviewer letter from the MHRA)...again I wondered why I had to do this…"
>
> ***Interviewer:*** How did you find out about the yellow card system?
>
> ***Husband* of P4:** "From the internet. I knew there was a body that regulated drugs, just through common knowledge, and I must have found out who it was…and I said, I asked at the hospital, and said why am I doing this, I wrote on the report… form that I filled in, I'm a 73-year-old man with Parkinson's, why should I have to do it, nobody else had done it, not the GP, not the hospital..."

From the extract above, it is clear that the husband of P4 felt that it should not have been his responsibility to report the ADR to the MHRA, but the job of the health professionals caring for his wife.

The majority of others, who were not aware that a patient reporting scheme existed, stated that they generally believed it was a good idea when they were told that such a scheme existed, although didn't have any particularly strong views on the subject.

A few survivors however, felt that such as scheme might undermine the authority of the medical profession, or believed that patient reports may not contain medically accurate information:

***P7 (21 year old male)*:** "I think it [patient reporting of ADRs] may undermine the authority of a doctor…like if he's treating you, you should trust him to treat you, and if you then report it, it almost goes above his head…"

Wife of P8: "Yes. I think, I'm a bit concerned about things being reported on the internet because how do you know whether, if you go to a GP and say "I've come out in a rash, because I think I've taken this new pill" or whatever it is, he would then ask the questions and decide whether [it is an ADR or not], but if you're just reporting it yourself, I don't know how accurate the information is. But I think in view of what happened to D**** (P8), I think I might do it, never the less."

2.4.2.6 Views on information sources regarding ADRs

When survivors were asked how they thought patients should be warned about the potential adverse effect of medicines, many felt that this should be done verbally, preferably by their GP or other healthcare professionals such as pharmacists. P1 for example, felt that this was particularly important in the case of the elderly or visually impaired:

> ***P1 (75 year old female):*** "They give you leaflets with your tablets, but if you've got someone like Mr T out there (P1 refers to her friend who has accompanied her) he's blind, so there's no way he's going to know what it says (laughs), so probably the doctor could give you a verbal warning…I know they don't have a lot of time and all that….but they could say 'it might give you a bit of sickness…or it may cause a bit of that...' for older people, for people who are getting older….and if you read everything on that leaflet (laughs) you could end up by having them all! (laughs) It's psychological isn't it!"
>
> ***Interviewer:*** Are you aware of any other trusted sources where you can get information about medicines?
>
> ***P1 (75 year old female):*** "No…..no…um… with the SJS naturally I always ask the chemist whether it's safe, is the drug safe and all that, and the doctor, who I think gets fed up with me asking …he must think, she must know, otherwise I wouldn't give them to her!"

Survivors of the ADR still trusted health professionals such as GPs as their primary source of information regarding medicines and ADRs as can be seen from the extracts below. However, as we have seen, this of course did not indicate that survivors always took the advice given to them.

> ***Interviewer:*** Who do you trust as sources of information on medicines?
>
> ***P7 (21 year old male)*****:** "Your GP, doctor, anyone with….like with the profession that should know really, because that's their job in a way, you should trust your doctor to tell you the things they should

tell you, because if you don't have that trust then you're looking at a third party to tell you…then it just shakes the trust in the whole system."

P5 (27-year-old female): *"*Well I would only take a medicine that I had bought from a chemist or was prescribed by a doctor and I would trust that information that I was given there."

Interviewer: Do you think the sources that are out there about medicines like leaflets are adequate, things that are on the internet and the leaflets, do they give information that you need do you think?

P10 (74 year old male)**: "**Again I suppose it depends whether you're looking for it, I have never really gone into anything like that. It's not something that I have ever really thought about. I suppose if I go to the doctors and am given anything I just accept that this is safe and ok to take".

Many felt that the patient information leaflets overloaded them with too much information regarding potential adverse effects, and that drug companies did so to avoid litigation. As a result, some survivors did not find such leaflets helpful in terms of helping them decide whether or not they should take a particular medicine, as illustrated by the interview extracts below:

Interviewer: Do you think the information sources for medicines are adequate?

P3 (65-year-old male)**:** "They're more than adequate if you read the slip with every medicine... you wouldn't take the damn thing if you've read it. It asks more questions than it answers when you read the disclaimer."

Interviewer: Right. How do you find the language within those leaflets?

P3 (65-year-old male)**:** "Legal. It just covers my backside. They're written that way and that is the way they have to write them, because the insurance companies then put the lawyers on to it, and you've got to have in legal speaking."

***P4 (70-year-old female)*:** "I do read them [patient information leaflets], they're scary because I often look at them and I trust that whatever I'm being prescribed is compatible; I've got such a lot to take I said to the doctor, when I have breakfast there are more pills on my plate than there is food!"

P8's Wife: "But every leaflet, I take a whole raft of pills and every leaflet has everything from constipation and diarrhoea to skin rash as a warning, so you know…"

***P8 (82 year old male)*:** "Well they're covering themselves."

The internet was cited as a useful source of information, and as discussed previously, was an important source of information at the time of the reaction both for survivors and their families:

***P4 (70-year-old female)*:** "I'm not internet conversant, because he's on the computer (points to husband), but children helped and daughter helped. They all went looking for [information]…"

***P13 (41-year-old male)*:** "You mean how to get information [about medicines], I would say internet definitely, because the doctors never really told my family the risks, it was he has Steven Johnson syndrome, it's a rare condition and that's where the bells rang and my sister went on the internet and looked it up, and told people, the doctors don't actually tell you the true risk side of things they keep it back because they don't want to scare anyone."

Interviewer: Do you think the information sources which are around, like the internet or elsewhere are adequate, do they give the information you need?

P13 (41-year-old male): "Oh yes because my sister did pick it up [on the internet], it actually told you everything up, it actually showed you pictures of people with scars as well. Pictures say more than words don't they?"

One survivor described that although she relied heavily on internet sources of information, she uses her own judgement to assess their reliability, and has 'different levels of trust' for different web-based sources:

> ***Interviewer*:** Where do you find the information on medicines then?
>
> ***P14 (48-year-old female)***: "Internet...everyone needs to know. I just found my GP Notebook now [an online medical reference resource for clinicians] that advises on that, don't get me wrong I don't believe everything on the internet...But I read it and go on different sites and understand it and then I diagnose myself."
>
> **Interviewer:** Are there particular sites you trust more than others?
>
> ***P14 (48-year-old female)*:** "I usually go on medicine net. I go on the NHS one...because it's got to be kosher...whereas [regarding] this new therapy [that the GP prescribed], different websites that I've been to all goes back to the one medical centre, I'm thinking, nah, there's something wrong".

P14 also describes the process she undergoes when deciding whether or not to take a particular medicine:

> ***P14 (48-year-old female)***: "The doctors will tell me [to take a medicine], so I'll say "Right, what's it for? What will it do?" And "What are the side effects?" And then I'll take what he's told me, then I read the leaflet and then I go on the net."

2.4.2.7 'Hindsight'

None of the survivors recalled being warned that SJS or TEN was a possible adverse effect prior to taking the drug. Some survivors however, were rather philosophical when asked whether they felt that they should have been warned, bearing in mind that the ADR was rare. They indicated awareness that many ADRs affect a minority of people. Interestingly, many stated that they would still have taken the implicated drug even if they had been warned, as all medicines are associated with a degree of risk, as can be seen from the quote below:

> ***P10 (74 year old male)*: "(**Sighs) Well it's just one of those things whatever medication you take has side effects and nobody knows how you are going to react to it do they who would have thought that would have happened to me you take them at your own risk in a way".

2.5 Discussion

2.5.1 Discussion of results

My interviews with survivors of SJS and TEN provided a rich source of data regarding their experiences (both positive and negative), their understanding and interpretations of why the ADR occurred, the impact of the ADR on their current life, and their views towards medicines. I will now discuss some of the themes and subthemes I identified through my study, explore the relationship between various themes, and discuss ideas and hypotheses based on my findings.

It is clear from my findings that survivors of SJS and TEN appeared to have a good recollection of their experiences and described a variety of circumstances which led to them developing the ADR. Some described being prescribed the culprit drug for illnesses which were serious in themselves if left untreated, and in general, all of those who were, understood that the drug causing the reaction was necessary at the time. Two survivors however, believed that that the culprit drug was unnecessary in the first place; this might be explained by the fact that both felt that the condition for which it was prescribed was minor and could therefore have been managed conservatively. This is an interesting finding, and it could be hypothesised that despite the experience of a life-threatening ADR, patients are generally accepting of the fact that the prescribing of the culprit drug was necessary and could not have been avoided if they believe that the condition for which it was prescribed was serious or would have a significant impact if left untreated. This may, in part, also explain why many of these survivors stated that they would still have taken the implicated drug even if they had

been warned of the potential risk of SJS or TEN. It could therefore also be hypothesised that individuals who have experienced an ADR undertake a type of harm-benefit analysis with hindsight after the event, and that the seriousness of the condition for which the culprit drug was prescribed is taken into consideration.

Many survivors did, however, believe that the ADR itself might have been avoided if the prescriber had acted differently. We know that there are only rare circumstances in which the risk of SJS and TEN can be predicted prior to treatment; for example, the increased incidence of carbamazepine-induced SJS in individuals of Han Chinese ethnicity with the *HLA–B*1502* genotype as previously discussed in 2.1.2. None, however, was relevant to my cohort of survivors. Nonetheless, survivors still formed their own interpretations of why the ADR occurred. Only two survivors believed that the reaction was unavoidable or idiosyncratic, and correctly understood that it could not have been predicted by healthcare professionals. The majority however, believed that the reaction was avoidable, and expressed views regarding why the ADR occurred, included medical staff ignoring existing allergies and being prescribed too high a dose of the drug. These beliefs appear to have influenced their current views and attitudes towards medicines and their trust in healthcare professionals. Those who believed that the ADR could have been avoided had less trust in medicines prescribed to them and in the healthcare professionals doing so. This is partly in keeping with previous research which has shown that patients' confidence in medicines appears to stem from an overall confidence in doctors, as discussed previously in Chapter 1 (Ipsos MORI & MHRA 2006).

Based on my findings, it could be hypothesised therefore, that individuals experiencing serious ADRs such as SJS and TEN form their own beliefs regarding why the ADR occurred

and how it could have been avoided, and that these may impact on their future trust in medicines and in those prescribing them. It could also be hypothesised that providing patients with accurate information regarding ADRs, particularly those that could not have been reasonably predicted such as SJS and TEN, is important to avoid misconceptions which may later impact on future trust. How this information might be provided, is discussed in Chapter 5.

Survivors (including those who did not have long-term sequelae) vividly recalled the initial symptoms they experienced at the time of the event, including extensive blistering, painful ulceration, and 'shedding of skin' resembling burns; this is perhaps unsurprising due to the traumatic nature of the ADR, and it could be hypothesised that their vivid recollection emphasises the significant impact that the ADR had on patients at the time of the event. Several also described how healthcare professionals initially failed to recognise the ADR, and recalled how their signs and symptoms were confused for other conditions, including viral illnesses. Despite this, survivors didn't apportion blame towards these healthcare professionals for the delay in their diagnosis (although some described perceiving their GPs as 'feeling guilty' as a result); it could be hypothesised that this was because survivors may have justified the delay that occurred due to their awareness that the condition was extremely rare (as evidenced by findings from my study), and hence more difficult to diagnose. Although there is currently little in the literature regarding how patients respond to a delayed diagnosis for rare life-threatening conditions such as SJS and TEN, we know that for others which are more common, such as meningitis or appendicitis, a delay in diagnosis is a common reason for litigation (Raine 2011).

Healthcare professionals were also perceived by many survivors to have limited knowledge about the condition and how to manage it, even after the diagnosis was made; survivors

however were less accepting of this. Nonetheless, they indicated that they preferred that health professionals were open and honest about their limited knowledge and the lack of definitive treatments available, and were keen to remain fully informed regarding progress in management and prognosis. Indeed, survivors' views on medicines and health professionals were more positive if they perceived they had been given clear and honest information at the time of their illness, and this is particularly apparent in the case of P14.

It is also clear from the current study that survivors who were managed in the specialist dermatology centre housing the burns unit (SOH) had a more positive experience, in that they felt better supported and managed than those who were managed in non-specialist centres. This was mainly because they felt that specialist centres had the appropriate facilities and staff to deal with the condition. These findings support existing objective evidence that early referral and management of SJS and TEN in a specialist unit leads to better outcomes, with reduced mortality and length of hospitalisation, as discussed in 2.1.6 (Chave et al. 2005;Kelemen et al. 1995;Mcgee & Munster 1998). It could therefore be hypothesised that as well as improving clinical outcomes such as mortality, managing patients with SJS and TEN in burns units may also improve patient experience.

The experience of a serious ADR had a significant impact on the current lives of survivors, both physically and psychologically. Their experiences also influenced their views towards taking medicines and their trust in health professionals. The experience of a serious ADR for example, had a profound impact on survivors' current medication taking behaviour, with many avoiding medicines altogether, or avoiding seeking medical attention when ill, regardless of the impact on their health. The harmful consequence of this is most clearly demonstrated with the example of P2, who, after developing TEN from lamotrigine for

newly diagnosed epilepsy, refused to take any antiepileptics after the ADR for a number of years as she was too frightened to do so. As a result, she suffered from at least two serious epileptic fits, which in themselves were life-threatening. Others also had unsubstantiated fears, for example, of food supplements, or medicated lozenges, showing that their fears extended beyond prescribed medicines, and possibly related to a lack of confidence in their ability to avoid a recurrence of the reaction. These findings indicate that patient education after the event may be very valuable. It would be important, for example, to explain to patients that those experiencing idiosyncratic adverse drug reactions such as SJS and TEN are not more pre-disposed to experiencing other unrelated ADRs as far as we are aware; this might be helpful in reducing avoidance behaviour related to necessary medications in the future.

Interestingly, some survivors did not appear to have negative views regarding the safety of the culprit drug in general, despite having had a serious reaction to the drug themselves. This was mainly because they were aware that although taking the culprit drug would be life-threatening for them, this would not necessarily the case for others. They believed that the reaction was specific to themselves and their individual circumstances. This is in keeping with my findings regarding their interpretations of why taking the culprit drug resulted in their ADR, for example, the belief that it was caused by being prescribed too high a dose of the drug, rather than the drug being 'dangerous' per se. Similarly, the majority indicated that their views on the safety of medicines in general had not changed since the reaction despite a change in their own medication-taking behaviour. This may be explained by the fact that the majority accepted that all medicines are associated with benefits and harms, and that these had to be taken into account when deciding to take medications. Survivors also believed that

harms from medicines could be minimised by only prescribing or taking medicines when they are absolutely necessary.

Survivors of the ADR not only experienced long-term physical sequelae such as cutaneous scarring, but also psychological effects, such as the general fear of medicines, foods etc as discussed previously, and a lack of confidence in their physical appearance due to scarring. One survivor (P13) also described symptoms of post-traumatic stress disorder (PTSD). This is perhaps unsurprising, given that the risk of PTSD is significant in individuals with any critical illness requiring intensive care, and also in those experiencing serious burn injuries, where skin loss and scarring sustained is similar to that seen in SJS and TEN (Cuthbertson et al. 2004;Patterson et al. 1990).

The same survivor also described how he felt 'let down by the aftercare' following his discharge from hospital, and felt he wasn't provided with the psychological support he needed to cope. Based on these findings, it could be hypothesised that psychological support for sequelae such as loss of confidence due to scarring and symptoms of post-traumatic stress disorder in the aftermath of life-threatening ADRs such as SJS and TEN may be beneficial, and that this should be explored.

Survivors were asked whether they knew that patients could report ADRs directly to the MHRA themselves via the Yellow Card Scheme. Only one survivor (P4) and her husband were aware of this, as they themselves had submitted a report at the time of the event. The lack of awareness of patient reporting schemes amongst survivors of the ADR is supported by findings of a recent survey of 2028 patients and members of the public, which showed

that although around one-quarter of respondents had experienced an ADR, fewer than 10% had heard of the Yellow Card Scheme (Avery et al. 2011).

Interestingly, P4's husband felt that submitting the report should not have been his responsibility, but should have been the responsibility of the health professionals caring for his wife. This might be related to his motivation for reporting the ADR in the first place, which although was not explored in detail, appeared to be related to obtaining further information about the ADR, which he felt that the healthcare professionals caring for his wife were unable to provide him with. This theory is further supported by his additional attempt to contact the drug manufacturer directly for more information at the same time, and is also in keeping with findings from previous research exploring patients' expectations of reporting to the Yellow Card Scheme (Avery et al 2011), as discussed in Chapter 1.

The majority of others who weren't aware that a patient reporting scheme existed, stated that they generally believed it was a good idea when told that such a scheme existed, although didn't have any particularly strong views on the subject. Interestingly, a few survivors felt that such a scheme might undermine the authority of the medical profession, or believed that patient reports may not contain medically accurate information. This is an interesting finding, as it is contrary to what we know from recent research showing that patient reports of ADRs may in fact be very useful, in that they are often richer in detail than healthcare professional reports, are more likely to describe the effects on patients' lives, and can generate new signals when combined with those from healthcare professionals (Avery et al 2011). These findings do however indicate that despite their experience, some survivors still trusted the authority of reports by healthcare professionals, over those made by patients.

Survivors were also asked how they thought patients should be warned about the potential adverse effects of medicines. Many felt that this should be done verbally, preferably by their GP or other health professionals such as pharmacists. They also felt that patient information leaflets were not useful, as they were used as 'disclaimers' by drug companies, and often overloaded them with information. It is clear therefore, that in general, survivors of the ADR still trusted health professionals such as GPs as their primary source of information regarding medicines and ADRs, compared to other sources. This is in keeping with previous research showing that almost nine in ten adults trusted doctors to provide accurate information about the risks and benefits of medicines, and that among the least trusted sources were pharmaceutical companies and government organisations (Ipsos MORI & MHRA 2006).

Survivors also felt that the internet was an additional useful resource for obtaining information about medicines and their adverse effects. In fact, at the time of the event, the majority of survivors and their families relied heavily on internet sources for more information, with a few contacting online patient support groups set up for sufferers of SJS and TEN. The study of online support groups for those who have experienced ADRs such as SJS and TEN is therefore a potential area for further research, and is thus the focus of Chapter 3.

2.5.2 Limitations

Due to the rarity of the condition and its high mortality rate, it was not feasible to undertake formal purposive sampling, and hence our cohort may not be representative. This might for example, explain why only one of the survivors interviewed described long-term ocular complications, despite the fact that we know that these can be very common. However, it must also be borne in mind that those with severe ocular complications resulting in visual impairment, may not have been able to read the study literature sent out to them during the recruitment process, and hence would have been less likely to respond. In addition, my findings cannot be generalised due to the qualitative approach used. This, however, is accepted, as the aim of my study was to generate hypotheses and ideas, rather than test them, and this aim was achieved through the approach used.

In addition, as this was a retrospective study, the potential for recollection bias exists, particularly in those who experienced the ADR many years previously.

Finally, the experiences and views of survivors of life-threatening ADRs such as SJS and TEN may differ from the experiences and views of those of other serious or potentially fatal ADRs. It may not be appropriate therefore to extrapolate my findings to patients who have experienced other serious ADRs.

2.5.3 Further research

Recruiting a larger sample of survivors of SJS and TEN by undertaking a UK-wide multicentre study, might allow a quantitative analysis of experiences and views, and this might be undertaken, for example, by using questionnaire-based methods. This might allow

the testing of some of the hypotheses I have proposed, and is discussed in more detail in Chapter 5. In addition, undertaking such a study prospectively might also minimise the potential for recollection bias; however, it is likely that many patients would be too unwell to participate during the acute event, and any analysis would have to be undertaken soon after they had recovered from the episode.

From my findings, we know that some survivors and their families sought advice from SJS and TEN patient support group websites; the study of such websites would therefore be a novel area for further research, and is thus the focus of my next chapter.

Finally, patient experience of other ADRs could also be explored, and may help build on what I have found through interviewing survivors of SJS and TEN.

2.5.4 Conclusions

Life-threatening ADRs such as SJS and TEN may continue to affect patients' lives long after the event. Patients' interpretations regarding why the ADR occurred differed, and this, along with their experiences at the time of the event, may have influenced their trust in healthcare professionals and in medicines in general. Clear communication during the acute phase of a serious ADR, and patient education and support after the event, may therefore be important. My findings could be used as a framework for understanding patient experiences of other serious ADRs, and to improve the future management of patients with the condition.

3 CHAPTER 3– AN ANALYSIS OF INTERNET-BASED PERSONAL DESCRIPTIONS OF EXPERIENCES OF STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS

A paper related to this chapter has been accepted for publication and is currently in press**:** Butt TF, Cox AR, Oyebode J, Ferner RE. Internet accounts of Serious Adverse Drug Reactions – a study of experiences of Stevens-Johnson syndrome and Toxic epidermal necrolysis. *Drug Safety* 2012 (in press).

3.1 Introduction

3.1.1 Background

National statistics show that in 2010, 30.1 million adults in the UK (around 60% of the population) accessed the internet every day or almost every day; this is nearly double the estimate in 2006 of 16.5 million. In particular, 'social networking' is a popular internet activity, with 43 per cent of internet users posting messages on social networking sites or on 'blogs' (Office of National Statistics 2010).

Accessing health information is a common reason for internet usage, with around one third of European and American consumers using the internet for this purpose (Eaton 2002). The internet is not being used to search for information about disease and treatment alone, however. It is also being used by disease-focused internet communities to organise their own experience base, seek advice, and provide support to others; in doing so, such groups in general, aim to improve the lives of those who have experienced a particular illness. Such

use of the internet is widespread in patients with cancer for example, with patients, either directly, or via friends and family, accessing websites including those set up by patient support groups, to find 'second opinions' and seek support and experiential information from other patients (Ziebland et al. 2004). Social connections may thus be enabled by such internet support groups, and these constitute a new forum of social support with largely unstudied potential (Davison et al. 2000).

Material posted on social networking and patient support group websites, often include patient narratives of their illness, and hence, may provide a rich source of data for researchers regarding patient experiences. In addition, such material has been used to identify health beliefs, common concerns, and the emotional needs of patients (Eysenbach and Wyatt 2002). Such web-based material has recently been used to study the experiences of those with serious illnesses such as cancer and HIV/AIDS (Dickerson et al. 2006;Kim 2009;Kinnane and Milne 2010;Mo and Coulson 2008;Mo and Coulson 2010;Overberg et al. 2010;Rozmovits and Ziebland 2004), but has not been previously used to study the experiences of those who have suffered the effects of serious ADRs.

3.1.2 Narratives of illness

The Oxford dictionary defines a narrative as 'a spoken or written account of connected events; a story' (Oxford University Press 2012). There are a number of features that are common to narrative as a linguistic form. Firstly, it has a finite and longitudinal time sequence, i.e. it has a beginning, a series of unfolding events, and an ending. Secondly, it presupposes both a narrator and a listener or reader, whose different viewpoints affect how the story is told. Thirdly, the narrative is concerned with individuals; rather than simply reporting what they do or what is done to them, it is concerned with how those individuals

feel. In contrast to a list of measurements or the description of the outcome of an experiment, there is no self-evident definition of what is relevant or what is irrelevant in a particular narrative. The choice of what to tell and what to omit lies entirely with the narrator (i.e. the person 'telling the story'), and the narration invites an interpretation from the listener or reader (Greenhalgh and Hurwitz 1999).

Narratives can provide meaning and context for the patient's experience of illness. In the diagnostic encounter, narratives encourage empathy and promote understanding between clinician and patient. They also encourage a holistic approach to management, and may be intrinsically therapeutic or palliative. In the context of research, exploring the patient experience through analysing narratives can help create a patient-centred agenda in medical management, and help generate new hypotheses as discussed in Chapter 2.

In the area of research, narratives of illness can be subdivided into those that are solicited, i.e. those that are purposefully sought by the researcher (such as the narratives of SJS and TEN I obtained through interviewing patients in Chapter 2, or narratives obtained through the use of questionnaires), and those which are unsolicited, i.e. those which are written at the instigation of the patient and not at the request of the researcher. Regardless of how little it may be directed, a narrative which is purposefully sought by the researcher will often be 'composed' in the knowledge that it will be read or listened to by a particular audience (Robinson 2001); it could therefore be argued that such narratives may contain bias, as patients narrating their experiences may attempt to only include that which they believe would interest the researcher. The study of unsolicited narratives, however, may remove this element of 'direction' or bias (O'Brien and Clark 2010).

In addition, narratives may be verbal (such as those elicited in my interviews of survivors of SJS and TEN in Chapter 2) or written (such as those which are printed, for example, in magazines, books, letters, etc. or in electronic form, for example, on the internet). Finally, narratives used in research may be published (for example, those in research journals or books), or unpublished.

3.1.3 Internet-based narratives of illness

In general, websites accessible to the public may be categorised, based on their function, into personal websites (those published and maintained by a private individual), commercial websites (those which are usually profit making for a business), government websites (for example, websites hosted by the MHRA and US FDA), and non-profit organisation websites (for example, those run by charities). Such websites may or may not require a subscription, or require the user to 'register' to access some or all of their content.

Unsolicited internet narratives or descriptions of personal illness can be found on personal websites (e.g. in the form of a personal blog), in postings on general social networking sites (e.g. MySpace, Bebo, and Facebook), or in postings on specific patient support group websites for the illness (Farmer et al. 2009). Solicited internet narratives of illness may form part of online databases or 'collections' of patient experiences such as those set up by charities or healthcare professionals. As well as providing support and information for patients, such databases can also provide qualitative data for researchers exploring patient experience of illness (Gonzalez-Heydrich et al. 1998;Herxheimer et al. 2000).

The interactive and dynamic nature of the internet means that many web pages containing narratives of illness represent far more than conventional illness narratives alone, because as previously discussed, individuals posting on such websites can also interact with others to make social connections, provide advice and support, and seek help.

3.1.4 Personal web pages and blogs

A personal homepage or web page can be defined as a web page that has been published and maintained by a private individual or informal small group, to contain content of a personal nature rather than on behalf of an employer or institution (Dominick 1999;Doring 2002). The content of personal web pages can vary, and may include biographical information, or the narratives of the experiences of the author.

A blog (short for weblog) is an example of a personal home page, and can be defined as a website containing dated entries or posts, presented in reverse chronological order (Miller and Pole 2010). Blogs once required programming knowledge to create, but with the emergence of free software, virtually anyone with an internet connection can create a blog. Many such websites are interactive, allowing visitors to leave comments and even send messages to each other, and it is this interactivity that distinguishes them from other, static, home pages.

Personal web pages or blogs detailing accounts of illness are often constructed by individuals for a number of reasons. Hardey (2002) analysed 132 personal home pages detailing accounts of personal illness. For the purpose of his study, personal homepages were defined as pages that were created by private individuals (as opposed to companies and

organisations) focusing primarily on the health and illness experiences of the author. He categorised home pages into four different types: the first consisted of home pages primarily constructed to explain the illness and consequent emotional changes ('My story and explanation'), the second contained web pages where the author was cast in the role of expert advice giver to others with the same condition ('My story and advice'), and the third category was based around a desire to promote a particular health regimen or approach to illness ('My story and my solution'). The fourth type involved selling products through the internet ('My story and my products and services') (Hardey 2002). In a separate study, Hardey also analysed the use and production of health information on the internet, and showed that users of health services themselves have become significant providers of health information and advice (Hardey 2010).

Miller and Pole (2010) analysed the content and characteristics of influential health blogs and bloggers (i.e. people who write blogs), to provide a more thorough understanding of the health 'blogosphere.' They identified 951 health blogs in 2007 and 2008, and found that they typically focused on bloggers' experience with a single disease or condition, or their personal experiences of healthcare professionals. Half were written from a professional perspective, one third from a patient-consumer perspective, and a few from the perspective of an unpaid caregiver.

3.1.5 Social networking sites and online support groups

The experience of illness may be a profoundly social one, with suffering eliciting strong emotions, and the desire to talk to others as a result. Through interpersonal exchanges, patients can develop an understanding of their illness. Over a course of a particular illness, patients may talk to friends, relatives, and healthcare professionals regarding their diagnosis and what treatment may entail (Davison, Pennebaker, & Dickerson 2000).The proliferation of online support groups and social networking sites over the last decade, however, has enabled individuals to contact and share their experiences of illness with individuals similarly affected, and whom they otherwise may never have had the opportunity to 'meet'.

Social networking sites may be defined as 'online spaces that allow individuals to present themselves, articulate their social networks, and establish and maintain connection with others' (Cain 2008).

Numerous social networking sites exist, the most popular being *Facebook, Myspace, and Bebo.* Such social networking sites are used frequently by patients to share their experiences of the investigation, diagnosis, and management of disease. At least 757 patient support groups have been identified on *Facebook,* for example, with a small proportion of these (18.6%) also classed as fundraising/charity groups. (Farmer et al 2009). *Twitter* is another increasingly popular social networking site, which also serves as a 'microblogging tool', in that users can also describe their current status in short posts distributed by instant messages, mobile phones, emails, or the web (Java et al. 2009). All the social networking sites described require the user to register with the site, although no fee for using the site is required.

3.1.6 Online databases of patient experiences

Other websites provide access to solicited collections or databases of patient experiences. *DIPEx* (Database of patients' experiences), for example, is a multimedia online database of patients' experiences, consisting of a collection of visually recorded interviews with patients about their experiences of a wide range of illnesses, and the concerns that they have regarding issues included prescribed medication and adverse effects of treatment (Herxheimer et al 2000). The website run by this charity has recently been renamed 'healthtalk online.org'. *Experiencejournal.com* is another website featuring children's experiences of chronic illness such as asthma, including accounts from parents and relatives (Gonzalez-Heydrich et al 1998). Finally, *PatientsLikeMe* is an online community in which patients with life-altering diseases not only share their experiences, but also share information about treatments and outcomes. Data inputted by patients regarding their experiences of an illness or treatment is organised into charts and graphs, allowing patients to gain an insight into the illness or treatment, identify patterns, and thus place their experiences in context.(Frost and Massagli 2008;Wicks et al. 2010;Wicks et al. 2008).

The 'databases' described are run by charities, with input from healthcare professionals to ensure that the information presented is as balanced as possible.

3.1.7 Quality of health information on the internet

There is marked variation in the quality and reliability of patient health information available on the internet. A number of studies have in fact shown that the quality of information on the internet for various conditions including inflammatory bowel disease, chronic pain, oral

conditions, cancer, and alcohol dependence is often poor, and that only a small number of websites provided accurate information (Corcoran et al. 2009;Guardiola-Wanden-Berghe et al. 2011;Khazaal et al. 2010;Langille et al. 2010;Lopez-Jornet and Camacho-Alonso 2009;Lopez-Jornet and Camacho-Alonso 2010a;Lopez-Jornet and Camacho-Alonso 2010b;Ni Riordain and McCreary 2009;van der Marel et al. 2009).

A systematic review of peer reviewed literature however, showed that there were few reported cases of harm associated with the use of health information obtained from the internet. The authors point out that although this may be due to an actual low risk for harm associated with the use of information available on the internet, the potential under-reporting of cases may have influenced their findings (Crocco et al. 2002).

3.1.8 Ethical implications of using unsolicited narratives from the internet

There are a number of implications to consider when conducting research using naturally occurring personal illness narratives on the internet, written at the instigation of the author rather than at the request of the researcher. The main considerations relate to the concepts of confidentiality, anonymity, and informed consent. Robinson (2001) proposed a model for decision-making about the need to pursue ethical approval when using unsolicited narratives from the internet; in general, if data such as unsolicited narratives are publicly accessible, and information recorded by the researcher is done in such a way that it cannot be linked to the subject/author (i.e. by omitting full names if authors have identified themselves) , informed consent from those posting their narratives and ethical approval of such a study may not be required (Robinson 2001).

3.1.9 Rationale for current study

From my previous findings in Chapter 2, it is clear that survivors of SJS and TEN, relied heavily on internet sources for information about the ADR, and that support group websites for the ADR exist, as a number described accessing them for advice.

In light of this, I felt that searching the internet might therefore provide a source of patient experience of SJS and TEN, and allow me to explore this area further.

From my search of the literature, it is clear that although the experiences of patients posted on the internet for serious illnesses such as cancer and HIV/AIDS have been previously studied, (Dickerson et al. 2006;Kim 2009;Kinnane and Milne 2010;Mo and Coulson 2008;Mo and Coulson 2010;Overberg et al. 2010;Rozmovits and Ziebland 2004), those of patients who have experienced serious ADRs such as SJS and TEN have not.

A study of patient experiences of SJS and TEN on the internet may be desirable for a number of reasons. Firstly, the internet might provide a larger study sample, and allow access to a greater number of patient experiences or descriptions of the ADR. This would be of particular value in the study of SJS and TEN in view of its rarity. Secondly, as we know from my findings in Chapter 2, the families of patients also relied on the internet to get support and advice from others; a study of the internet might therefore allow an exploration of the experiences of family and relatives also. Thirdly, it might allow the study of unsolicited narratives or descriptions of the ADR, the advantages of which I have discussed previously. Using a different source to collect qualitative data might allow the identification of new themes not found through solicited methods (i.e. through directly interviewing survivors as described in Chapter 2). In addition, obtaining data regarding patient experiences through internet narratives might allow a 'triangulation' of the findings from my

previous interview-based study, where triangulation is defined as 'the combination of two or more data sources, investigators, or methodological approaches in the study of the same phenomenon' (Jick 1979;Thurmond 2001). Finally, similar to the findings of studies examining internet narratives of other serious illnesses (Ziebland et al 2004), an analysis of internet narratives of SJS and TEN may allow an exploration of why such individuals post on the internet, and the common concerns that they have.

In my current study, I therefore searched for unsolicited internet narratives or postings of individuals who identified themselves as having personal experience of drug-induced SJS or TEN, where 'internet narratives' were defined as first person descriptions written by a patient, relative or friend; and 'internet postings' as contributions made to a 'thread' of discussion on an internet site. I aimed to interpret the reasons for individuals posting on internet sites, explore the concerns that they had, and undertake a comparison of themes identified from internet narratives with those found through interviewing survivors of the condition 'face to face'.

I also undertook a descriptive analysis of narratives, including an analysis of narrative author demographics, an expression of awarene**ss** of the cause of the condition, and whether or not authors mention the drug responsible for causing the reaction.

3.2 Aims

1. To identify unsolicited internet narratives or postings of individuals with self-identified personal experience of drug-induced SJS or TEN, on websites accessible to the public.

2. To interpret the reasons why such individuals post on websites.

3. To explore the questions and concerns that these individuals have.

4. To determine whether themes identified in internet narratives of SJS and TEN, differ from those elicited through interviewing survivors of the condition.

3.3 Methods

3.3.1 Ethical approval

Ethical approval was not required for this study, as only anonymised data would be collected from publicly accessible websites, as previously described.

3.3.2 Data collection

I was aware of the existence of one website, *www.sjsupport.org* that contained unsolicited narratives or postings of those with personal experience of SJS or TEN. I then identified other websites in the public domain by using popular internet search engines *Google*, *Google Blog, Bing, Yahoo, and Ask Jeeves*. I also searched social networking sites *Facebook, Twitter, Bebo, and MySpace.* Searches were performed using the keywords [*Stevens-Johnson syndrome* OR *Stevens Johnson syndrome* OR *Toxic Epidermal necrolysis* OR *SJS* OR *TENS* OR *Lyell's syndrome* OR *adverse drug reaction(s)* OR *medication(s)* OR *side-effect(s)*] in combination with keywords [*patient experience* OR *personal experience patient illness* OR *personal illness* OR *blog* OR *patient story (ies)* OR *patient account(s)* OR *patient narrative(s)*].

Data were collected during two periods: February 2009, and again in June 2010 to look for additional data available since the period of first data collection. Having identified relevant websites, I then examined the patient descriptions.

Inclusion criteria

'Narratives' for the purpose of my study, were defined as first person descriptions by a patient, relative or friend; and 'internet postings' as contributions or responses made to a 'thread' of discussion on an internet site. Each contribution to the thread was counted as a unique internet posting. The term 'internet description' was used to encompass both narratives and internet postings. Only unsolicited internet descriptions written in English and where there was evidence of self-identified personal experience of SJS or TEN (either as a patient or as the relative or friend of a patient) were selected and included in the study.

Exclusion criteria

I excluded non-written accounts, such as video presentations; internet descriptions written in languages other than English; and descriptions that did not reflect personal experiences as a patient, relative or friend (e.g. those posted by healthcare professionals or carers).

All internet descriptions that met the inclusion criteria on the identified websites were downloaded, and each was assigned a numeric code. Internet descriptions from each website found were copied and pasted in their entirety into Microsoft Word; they were not edited for spelling or grammar or otherwise, but full names and contact details were omitted if authors had identified themselves or others. These were then imported into the qualitative software package NVivo 8.0 (QSR International) which was used to manage the coding of text within transcripts, and for organising passages from text into themes and subthemes.
Descriptive data such as the author's country of origin was entered into a Microsoft *Excel* spreadsheet.

3.3.3 Analysis

Descriptive analysis

Descriptive data extracted included the role of the author if provided (i.e. patient, relative or friend of patient), the gender and age of the patient at the time of the reaction, country of origin, an indication from the internet description of whether or not the author understood or believed the reaction to be drug-induced, and the medicine responsible if mentioned. Each internet description was also analysed to interpret the apparent reason or motive for posting the description on the website.

A word frequency analysis of internet narratives for words and terms used to describe their experiences was also undertaken by a co-researcher OM, using a linguistic analysis program created by the Department of English at the University of Birmingham (Mason 2009).

Qualitative analysis

I also undertook a qualitative analysis of internet descriptions using 'thematic analysis' methods. Thematic analysis is a method for identifying, analysing, and reporting patterns (themes) within qualitative data (Braun and Clarke 2006). It differs somewhat from the 'grounded theory' methods I employed in Chapter 2, in that although both methods seek patterns or themes within data, the main aim of grounded theory analysis is to generate a plausible and useful theory of the phenomena that is grounded in the data. In thematic analysis however, researchers need not subscribe to the theoretical commitments of grounded theory methods, and can just report experiences, meanings, and realities of participants.

Themes or patterns within data can be identified in one of two primary ways: in an inductive 'bottom up' approach, or in a deductive 'top down' approach. An inductive 'bottom up'

approach means that the themes are strongly linked to the data themselves (and as such, this form of thematic analysis bears some similarity to grounded theory). Inductive analysis involves coding data without trying to fit it into a pre-existed coding framework or the researcher's analytical preconceptions. A deductive 'top down' approach however, allows the mapping of themes found in the data, to a pre-existing coding framework found through previous research in that area; this approach tends to provide a less rich description of the data, but allows a more detailed analysis of some aspects of the data.

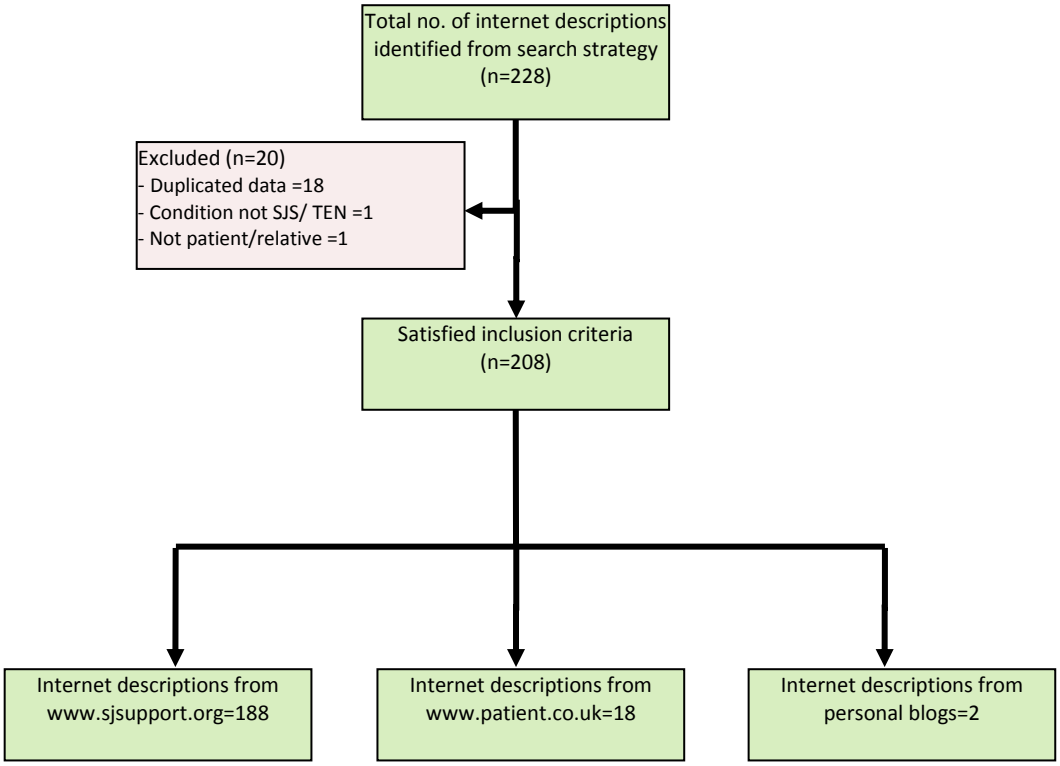
In the current study, I used both inductive and deductive methods of thematic analysis. I used a 'top down' deductive approach to map themes from this study onto themes identified from my previous qualitative analysis of interviews with survivors in Chapter 2. I also identified novel themes not previously found in my face-to-face interviews. Novel themes and subthemes were then grouped together using an inductive, 'bottom up' approach.
I analysed all narratives both for pre-existing and novel themes, and ensured consistency through blind dual coding of a randomly selected subset of twenty narratives with a second researcher (ARC); any variations in coding were resolved by discussion to achieve consensus. A third and fourth researcher (REF and JO) also analysed emerging new themes to ensure rigour in the analysis. I then elaborated the final coding scheme.

3.4 Results

3.4.1 Identification of internet descriptions

By using the internet search engines described, I identified two major websites *(http://www.sjsupport.org* and *http://www.patient.co.uk,* accessed June 2010) and two blogs (*http://www.joeway.co.uk* and *http://www.milnesjs.com*, accessed June 2010) containing relevant internet descriptions. A total of 228 internet descriptions related to personal experiences of SJS and TEN were identified and downloaded, of which twenty were excluded (see figure 3-1), leaving 208 descriptions for analysis. Although patient support groups for SJS and TEN were identified on social networking site *Facebook*, no internet descriptions meeting the inclusion criteria were found on this, or on *Twitter, Bebo* and *MySpace.*

Figure 3-1: Identification of internet descriptions



Of the 208 postings included in the study, the majority (188) were downloaded from an international SJS support group website (*www.sjssupport.org*). Eighteen were downloaded from *www.patient.co.uk*, a website providing an interactive patient forum for sharing experiences of medical conditions, and two narratives were downloaded from personal blogs.

3.4.2 Descriptive analysis

Demographics of internet description of authors

A total of 139 narratives were posted by those who had directly experienced SJS or TEN and 69 by relatives; one was jointly submitted by a patient and a relative. Of those posted by relatives, thirty were posted by mothers. Table 3-1 shows the relationships of relative authors to the patient.

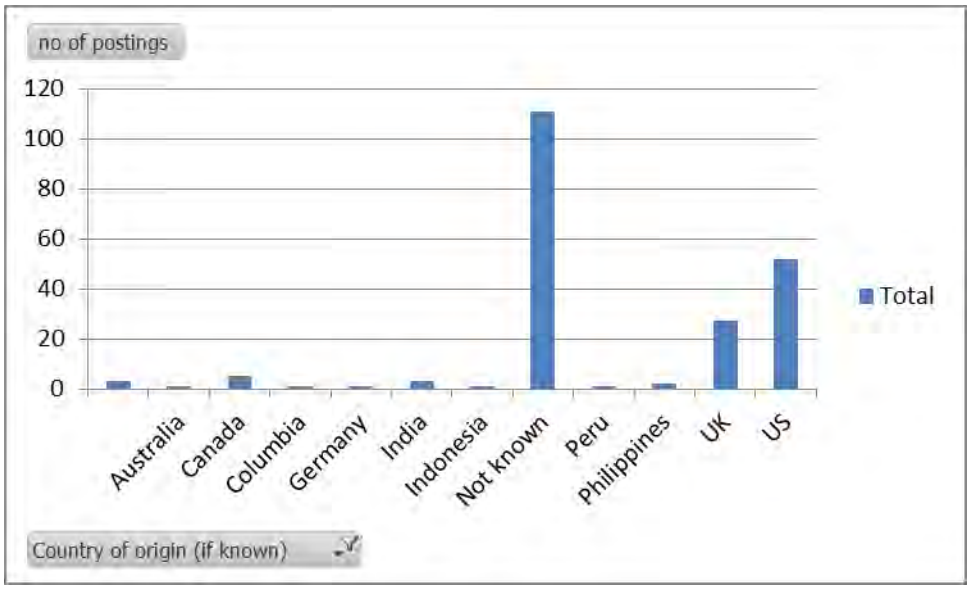
Table 3-1: Relative author demographics

Relationship of relative poster to patient	***No***
Mother	30
Father	8
Parent	7
Daughter	7
Wife	4
Sister	3
Brother	2
Fiancé	1
Girlfriend	1
Granddaughter	1
Great Aunt/Uncle	1
Husband	1
Mother in law	1
Sister in law	1
Uncle	1
Total	*69*

The authors of 128 of the internet descriptions indicated that they were female and 68 that they were male. 125 authors (88 patients and 37 relatives) indicated the age at which the reaction occurred. The mean age at the time of the reaction was 17.5 years, with a range of 3 weeks to 77 years, and bimodal ages of 3 and 8 years. Many patient-authors had developed the condition as children and described their experiences retrospectively.

Fewer than half of the authors indicated their country of residence (97/208); the majority of these lived in the United States (52/97), and a further 21 indicated that they were from the UK (See figure 3-2).

Figure 3-2: Indicated country of residence by authors



Causes of SJS and TEN

Together with a second researcher (ARC), I reviewed all internet descriptions to determine whether authors indicated a likely cause for the condition. 152 internet descriptions (73.1%) indicated that the condition was likely to be drug-induced; in 38 descriptions (18.3%) the

cause was not absolutely clear. The condition was unlikely to be related to drugs in eighteen descriptions (8.6%) (Viral causes, including *Herpes simplex* and mycoplasma infections were mentioned in five cases), and we did not analyse those descriptions further.

The specific culprit drug was mentioned in 135 descriptions where a drug cause was suspected, and of these, sixty referred to the culprit drug by its brand name. Eight descriptions mentioned the general drug class implicated only (e.g. 'antibiotics'). Multiple drugs were implicated as causes of the ADR in twelve descriptions. Table 3-2 shows the commonest culprit drugs detailed in postings.

Table 3-2: Culprit drug indicated in internet description

Commonest culprit drug	***No of postings***
Sulfonamides	31
Penicillins	19
Ibuprofen	8
Carbamazepine	7
Macrolides	7
Cephalosporins	7
Phenytoin	7
Lamotrigine	7
Tetracyclines	5

Motives for submitting an internet description

We categorised internet descriptions according to our perception of the motive for submission to a website, on the basis of statements made by authors within internet descriptions. We identified four major reasons. The first was individuals wishing to share their experiences and provide support for others (164). Secondly, patients or their relatives

asked for advice from others regarding the condition and its complications (33), and the third category both asked for advice and wished to share experiences (10). Finally, one requested funds to treat the complications of SJS/TEN (1). (See Table 3-3 and 3-4)

Table 3-3: Motivation for posting on website

Motivation for posting	***No of internet descriptions***
Sharing experience and support for others	164
Advice	33
Advice *and* sharing experience/support for others	10
Request for funding	1

Table 3-4: Examples from internet descriptions indicating motives for posting

Motivation for posting	***Example***
Advice	Internet description 40: *"Three weeks ago my son got Stevens Johnson syndrome and now he has developed diabetes type 1. He is 22, 6ft 7 inches and very fit. Has anyone heard of a correlation between the two?"*
Sharing experience and support for others	Internet description 3: "*Thank you for letting us share our story of our experience with Stevens-Johnson Syndrome. We hope that this may help someone else that may be going through the same thing, and our prayers are with you all".*
Advice *and* sharing experience	Internet description 137: "*I am presently going through a allergic reaction to bextra [valdecoxib], i think i have sjs, i have many of the symptoms listed, severe skin rash, blisters, breathing problems at times...i have been to more doctors, have had two mri.cat scans but no one seem to have a clue what is causing this.i wonder if any of your members could give me some guidance..."*

Word frequency analysis

Table 3-5 shows words used by internet description authors to describe their experiences in order of their frequency. Description authors most frequently used words such as 'blisters', 'reaction', 'pain', 'rash', 'drug', 'infection', 'medication', and 'allergic' in internet descriptions of their experiences.

Table 3-5: Frequency of words used by authors in internet descriptions

Words used by internet authors in internet accounts	***Total no. of times mentioned***
'SJS'	391
'Hospital'	362
'Doctor' or 'Doctors'	532
'Mouth'	236
'Eye' or 'Eyes'	376
'Skin'	201
'Blister' or 'Blisters'	231
'Pain'	160
'Reaction' or 'Reactions'	163
'Rash'	118
'Drug' or 'Drugs'	150
'Medication' or 'Medications'	131
'Antibiotic' or 'Antibiotics'	94
'Allergic'	86
'Swollen'	69
'Burn' or 'Burns'	81
'Lesions'	44
'Bactrim' (Co-trimoxazole)	36
'Scars'	30
'Penicillin'	29

3.4.3 Qualitative analysis

3.4.3.1 Themes similar to previous interview-based study

I was able to map several themes from internet descriptions, directly onto those found in my earlier analysis of face-to-face interviews with survivors of SJS/TEN using a 'top down' thematic approach (See Chapter 2, figure 2-1).

These included their experiences of the condition and its impact on their current life, including long-term physical complications such as scarring and avoidance of medicines. In contrast to the interviews with survivors however, the internet accounts did not shed much light on patients' interpretations regarding why the ADR may have occurred.

Experiences of the condition

Similar to the findings from my interview based study, description authors recalled how their signs and symptoms were initially confused for other conditions such as chicken pox or sexually transmitted diseases. Patients and relatives describe the distress they felt when they were misdiagnosed. In some cases, the diagnosis offered was associated with considerable stigma and affected personal relationships, for example, diagnoses of sexually transmitted diseases, as can be seen in Internet description 133. In other cases, they believed that their concerns regarding a serious cause for their symptoms were dismissed by healthcare professionals, as can be seen from the extracts below. In the majority, misdiagnosis resulted in a delay in getting the correct diagnosis and treatment.

Internet description 133: "The fever comes and goes. I asked her to check my genital area as no other doctor has. She ran a full battery of tests and reviewed the lab results from my ER visit the night before. The blisters are now covering my lips and mouth, down my throat, in my ears, nose, and vagina. She tested me for every known STD [sexually transmitted disease]. After enduring an extremely painful vaginal exam, she told me she wanted to treat me for Herpes. As you can imagine, this has caused great stress on my marriage."

Internet description 136: "As the doctor diagnosed me with things like chicken pox, measles, and flea bites my mom looked frantically through a book of medical problems and came to Steven Johnsons Syndrome. It fit the description perfectly but when she asked the doctor if it could be that he said no, it's too rare."

Internet description 162: "The DR [doctor] came back with his diagnosis, he said it was 'psoriasis'. I knew in my gut this guy was way off. He prescribed Justin a new antibiotic told me to give him ibuprofen and Benadryl [diphenhydramine] and sent us home..."

Patients also described how they felt that they had 'turned into a monster', and how others reacted in a negative way to the change in their physical appearance as a result of the ADR. In a few cases, this resulted in social isolation, and in others, had a significant impact on personal relationships, as can be seen from the extracts below:

Internet description 11: "I remember blisters all over my body that itched and burned constantly. I remember my little sister thinking that her big sister had turned into a monster."

Internet description 61: "Close friends told me later that they found it very distressing coming to see me as they really thought that I was going to die mainly because of the way I looked."

Internet description 69: "My wife was brave thru this ordeal, but she no longer found me sexually pleasing because of the sight… We are just beginning to make head way in our relationship."

Internet description 73: "I could see the look of disgust on the face of my aunt and my wife and the visitors for what was happening to me. Everyone who saw me could not believe the way I looked like. Even my kids when they visit me could not recognise me as if I was turned into a monster."

Internet description 124: "...and the day when I'll be released from the hospital finally came... after 1 1/2 months. What I looked like that time made people a little disgusted and scared. I still have scars, I didn't have nails, and only a little hair were left. I had no friends in elementary [school]... so I just concentrated on my studies. I don't stay quiet when my classmates make a fool out of me. I stand up for myself. I learned the harshness of life at a young age..."

Impact of the ADR on current life

Similar to my study in Chapter 2, experiencing the ADR had a profound impact on authors' current lives in various ways. Many, for example, stated that they now avoided all medicines in general due to a fear that they might cause a recurrence, as can be seen in the internet quotes below:

Internet description 92: "...in the mean time, we live one day at a time, suspicious of all meds, suspicious of all foods, and even suspicious of the air that James breathes....why, why, why???"

Internet description 203: "Unfortunately I don't know what drugs he was given in either event, but he refuses (as he MUST) to fill or take any sort of prescription medications."

Others felt that better warnings might have allowed them to avoid the offending medication in the first place, as can be seen in this extract:

Internet description 204: "I just wish the FDA [Food and Drug Administration] / Doctors would warn consumers. If I had known that such a horrible syndrome existed I would have done anything in my power to avoid medications."

Finally, similar to survivors interviewed, many described how they coped with the long-term physical complications of the ADR, such as scarring and disfigurement:

> ***Internet description 42:*** "...i'm 21 years old. I had a severe case of SJS when i was five years old. I live in Southampton, England and when i had it no-one knew what it was. I still have scarring on the back of my legs because my skin kept sticking to the bed sheets and i have a few marks on the side of my face..."

> ***Internet description 80***: "I am a 29 year old African American Woman who suffered from SJS in 1988. Like alot of other stories I've read, I was also initially misdiagnosed with the flu. However, after being admitted into the hospital, I was eventually diagnosed correctly and transferred to Kosair Children's Hospital's burn unit. I was in the hospital for about 2 months and my memory of the hospital stay is very faint because I was on morphine during most of my stay. However, as a result of this syndrome, I now have permanent scarring on most of my face, back, chest, and arms. I also lost my fingernails and toenails permanently. It gets hard sometimes to face people because they stare and wonder what happened to my skin."

3.4.3.2 Novel themes

In addition to the above, six further major themes and three marginal themes were identified from the internet descriptions (see figure 3-3). Many of these relate to internet authors seeking advice from others who have experienced the condition, and the concerns that patients and their relatives have regarding SJS/TEN and its complications, and the desire to help others by sharing their story.

Figure 3-3: Novel themes and subthemes identified from internet descriptions

Theme	Subthemes
Seeking advice from others	• Am I a carrier of SJS/TEN? • What can I do to prevent recurrence? • Is there a food cause? • Is this symptom due to SJS? • Could his death have been prevented? • Did doctors miss telling me anything? • Effects on fertility • Information regarding ADRs in general • Is there a specific test for ADRs? • Could I get compensation?
Fears and concerns	• Is my other condition related? • Fear of effect on pregnancy • Fear of recurrence • Fear of sterility • Concerns that specific drug cause unclear
Physical complications	• Blindness • Genital involvement • Hearing loss • Photophobia
Desire to raise awareness	• Amongst healthcare professionals • Amongst the general public • Reporting a new drug cause
Helping others by sharing story	
Support from the stories of others	
Marginal themes	• Self diagnosis of condition • Lack of information at time of event • Social complications

Seeking advice from others

Many of the description authors explicitly sought information and advice from others who might read their posts. The topics on which they sought information were varied, and included seeking advice about the immediate cause, symptoms, and treatment of the condition.

Interestingly, authors also queried whether the reaction might be hereditary and described the fears they had for their children:

> ***Internet description 216***: "I'm totally clueless about SJS though. Am I now a carrier? I'm aware of the fact it was due to an allergic reaction to the drugs prescribed to me. I think I was extremely lucky as it only affected my mouth and not the rest of my body…Could anyone update me on what happens now with regards to SJS and me being a carrier? I'm aware I shouldn't use that medicine ever again though!"

> ***Internet description 70:*** "I gave birth to our son September 13, 2002 and am looking for information on heredity and drugs known to cause SJS, as everything I've read says it is genetic and blood relations have a greater chance of developing SJS. I cannot imagine anyone having to go through that, and need to protect my son. If anyone has any information please email me..."

> ***Internet description 108:*** "I would like to know more about my bout with SJS (which appears to be TEN after I have read more stories) but my father and mother have both passed away and my brothers and sisters really don't recall all the details…my interest now is borne from my concern that there could be some hereditary reaction that I passed along."

Others asked for advice on obtaining compensation for the drug-related event, implying a belief that the ADR should not have occurred and could have been prevented:

> ***Internet description 171***: "In the early eighties I suffered from this syndrome because of drugs that I was given during an operation. I was never told that I could die. My parents told me after 4 weeks of quarantine. The doctors took pictures. I was so upset and could not see my eyes were closed... I have just been informed that I should be compensated because I still have problems and I am looking for help."

Finally, a few authors asked others for general information regarding the ADR as they felt that they were not given sufficient information at the time of event, and wondered if their doctor had missed giving them important information:

> ***Internet description 39:*** "I had never heard of Stephens Johnson syndrome and nothing was ever mentioned to me of this disease until after my discharge from the hospital, I found this website while searching allergic reaction to Sulfa and when I inquired with my doctor, they stated that this was their diagnosis…I would love to hear from anyone similarly affected as I am wondering where I go from here and if there is anything else the doctors missed telling me."

Fears and concerns

Many authors expressed fears, for example, that the condition may recur, or that the term 'syndrome' meant that the condition was permanent:

> ***Internet description 34:*** "I will never forget. I feel traumatize and sometimes I feel very afraid that this might happen again."

> ***Internet description 71:*** "I am still quite confused by this syndrome. Will it stay in her system forever? Since it is a syndrome, does it always come back and never go away? I don't know anymore and I am scared for my daughter, please help."

Other authors had concerns that the ADR was linked with the development of other illnesses, although there is little current evidence in the literature for these associations:

> ***Internet description 40:*** "Three weeks ago my son got Stevens Johnson syndrome and now he has developed diabetes type 1. He is 22, 6ft 7 inches and very fit. Has anyone heard of a correlation between the two?"

Internet description 37: "I have suffered from depression which now it turns out may be as a result of the hypoglycemia which may be a result of a unfavorable reaction with a sulfa drug…I am concerned that the health problems I am having now are something that could be related to my SJS from 11 years ago."

Internet description 60: "Since then my health has not been the same. I was in nearly perfect health before. I rarely saw a doctor. Now I suffer from arthritis, tendonitis, and unexplained nerve damage in my wrist with muscle deterioration. As well as fatigue, insomnia and overall joint stiffness. I am not sure if these symptoms are SJS related but I feel as if they are. I would like to hear from anyone who has had unexplained ailments and thinks it may be SJS related."

Internet description 72: "I have severe degenerative disk disease and am slowly losing mobility and function. Accepted causes for my toasted disks are congenital or childhood inflammatory disk infection. Well, no one - on any side of the family - has disk problems and I never had an inflammatory disk infection. So my money is on the SJS causing a great chunk of damage when I was a child."

Finally, a number of female authors had fears connected with future fertility and pregnancy:

Internet description 25: "My parents told me the doctors expected side effects to be along the lines of blindness, deafness, or sterility. Thus far I can see and hear just fine, but I'm a 19 year old virgin, and I still live with this fear in the back of my mind that I might not be able to have kids when I'm ready to. I wish there were some way I could know for sure. I cry myself to sleep at night sometimes just thinking about never being able to have kids and not by my own choice; that the gift of bringing life into this world was taken from me. I pray it isn't so but not many people recover from SJS with no long term effects."

Internet description 148: "If anyone wants to e-mail me please do I would particularly like to hear from women who would like to have children to see if SJS effects fertility or blocks fallopian tubes as am thinking about trying for a baby soon before it's too late (I'm 34). I am one of the lucky people the only lasting effects I have (that I know of) are scars & bad eyesight & hearing. If people could please get in touch it would be appreciated..."

Physical Complications

In addition to extensive scarring, those experiencing the condition described other physical complications which were not identified through interviewing survivors of the condition, including severe visual impairment and sexual dysfunction:

> ***Internet posting 5:*** "On her first Birthday I was told my baby was going blind. I watched in horror as doctors performed traumatic procedures on my daughter to save her sight. Glass rods swept under her eyelids as I held her down. I wasn't supposed to let anything bad happen to my child no less hold her down while someone hurt her. She was terrified of everyone. Julie did lose all of her sight in her right eye and has low vision in her left. She has dry eye syndrome, photophobia and has had 8 lid entropian surgeries. She has attended preschool for blind children."

> ***Internet description 11:*** "I was finally mainstreamed into the public school system in the first grade where I was taught Braille, cane travelling skills, and many other important skills to being a functional and successful blind person. SJS damaged my eyes quite severely."

> ***Internet description 79:*** "... So now, 13 years later [after SJS], I am finally married to a very understanding wife but to be honest, our sex life is not what it could or should be simply because I cannot enjoy sex or achieve orgasm - lack of sensitivity on my part…I just don't know what to do about this and would dearly like to hear from anyone who may have experienced a similar experience. You know, if my arms, feet, toes, fingers or legs would have blistered and ruptured, I could have dealt with that …I really feel that it has left some long term effects that I will never overcome."

Desire to raise awareness

A number of authors discussed their desire to raise awareness of drug-induced SJS and TEN, not only among the general public, but also among healthcare professionals, as they believed that their condition had been misdiagnosed, or the diagnosis had been delayed**.**

> ***Internet description 150***: "I don't want people to suffer this complex disease, especially suffer unnecessarily due to ignorance, health money managers, and drug companies…Let's be honest, SJS

situation always has the potential for fatality. There is no little SJS case. I personally commit in any way to mobilize this [internet] group to grow, and to unify this community... I will work to raise funds or distribute information to aid the awareness movement."

Internet description 195: "I definitely feel that the medical profession is not aware enough of Stevens-Johnson. Every time I get a chance to tell my story to a medical person, I do. I wish there was a way we could tell our stories. I wrote to Oprah once in the hope that someone there might take an interest in our plight but did not hear anything from them. We need a way to educate the public about this terrible disease."

Internet description 147: "One of the things that didn't bother me about the whole ordeal that I thought would is being used as an example of an illness for student doctors. Sometimes there would be seven or eight students in my room at a time, and it didn't really bother me at all. I figure that as long as there are more medical professionals learning of this, then less people have to suffer as badly. It's such a scary thing…and I didn't even have it that bad. My heart goes out to anyone who has this, no matter how "bad" of a case it may be."

Internet description 199: "…kindly pass this mail to everyone that you know. Please be aware of what tablets you take, LIFE IS VERY PRECIOUS."

Self diagnosis

Authors described how they researched their symptoms when they developed the ADR, and attempted to reach a diagnosis themselves. In keeping with the views of survivors elicited through interviews, many were also surprised at the lack of awareness of healthcare professionals regarding the condition:

Internet description 67: "I started doing my own research and found a description of erythema multiforme in the Merck Manual of Medical Information. By the next evening, I recognized that I was starting to have lesions in my esophagus, eyes, and lips and went to the ER. I told the doctors what I expected and was started on high doses of Decadron [dexamethasone]... I was amazed at the lack of knowledge on the part of the medical professionals. I clearly knew more about this disorder than

anyone else I dealt with. I do however credit the ER doctor with listening to me and starting the steroids immediately."

Internet description 136: "…my mom looked frantically through a book of medical problems and came to Steven Johnsons Syndrome. It fit the description perfectly but when she asked the doctor if it could be that he said no, it's too rare ..."

Internet description 79: "To be honest, I was scared to death. I had no idea what could have caused this to happen and kept thinking that even though I was not a sexually promiscuous individual, perhaps I had contracted some type of sexually transmitted disease... I became very concerned and immediately drove to a nearby library and did some research - the only thing I could find that perhaps resembled what I had was syphilis."

Helping others by sharing story

A number of authors demonstrated a degree of altruism and the desire to help others by sharing their story on internet forums:

Internet description 37: "I feel so incredibly fortunate to not have had to suffer as much as some of these other people. I share my story so that it might help someone else. Until this website I had never heard of another person with this condition and had not ever found any real useful information concerning it."

Internet description 78: "My Father wants other people to know about this deadly syndrome, for people to be cautious of the drugs they take and for people to be aware of erring doctors. This is why I am sharing my brother's story with you. Who knows, this email may save a life."

Support from the stories of others

Others indicated their gratitude for the support and comfort they gained from reading the stories of others who had been through similar experiences.

> ***Internet description 4: "***I want say that in 1995 I tried to find any information I could on SJS and there wasn't much out there to find. A year ago I noticed that there is much more info on this syndrome. I am grateful for the info and I read alot of people's stories to Jeff it makes him feel not so alone.!!! Thanks for listening to our story."

> ***Internet description 90: "***We were later informed that this was a case of Stevens Johnson syndrome. His skin is still falling off and he is in so much pain I want to cry when I see him. I know nothing about this illness and I am thankful for this site. Your stories were heart breaking and I hope my brother's doesn't worsen. Please contact me with any useful information that could put my mom and myself at ease."

Reporting a new drug cause to other users

One author describes developing SJS secondary to *Zocor* (simvastatin) and explicitly indicates his desire to report to others what he considered a new ADR, although SJS is listed in Zocor's *Summary of Product Characteristics* as an adverse effect:

> ***Internet description 194: "***On Thursday I made an appointment with my doctor, and he was smart enough to not only realize my condition was caused by a drug reaction, he also mentioned Stevens Johnson Syndrome, although he didn't make a big deal about it. He took me off the Zocor immediately…It seems, after reading your website, that I was extremely lucky, not only to have such mild symptoms, but also to have a doctor who knew what he was doing. That's my story. I don't know if this helps you at all, but it might help to add Zocor to the list."

Social complications

Authors describe the social consequences resulting from disability due to the complications (or treatment) of SJS/TEN, indicating the burden resulting from the disease long after the event.

> ***Internet description 155: "***He stated that I had SJS and they began giving me Prednisone and I have been taking it ever since. Over the past few years many things have been going wrong with my health; diabetes, cataracts, polyperiphial neuropathy, weight gain, mooning of the face, mood swings, broken bones and the list goes on. I have been fighting with the VA and Social Security to get the benefits that I deserve and the fight goes on. I have lost several jobs and it is becoming increasingly difficult to provide for my family."

> ***Internet description 1:*** "My friends left me alone. They did not want any thing to do with me. There was this one word, which was following me every moment. That word was "Disabled and Handicapped"."

Lack of information at the time of the event

Finally, many patients and their relatives describe how they had difficulty in obtaining useful information about the ADR, particularly from the patients' perspective, and hence found support group websites helpful as evidenced by the extracts below. One patient describes how this provided her with the motivation to post her experiences on the internet:

> ***Internet description 189:*** "I spent almost 3 weeks in hospital, recovering from Stevens Johnson Syndrome...While I was in there, I tried to get friends to get information for me about Stevens Johnson Syndrome, and I was very surprised by the lack of information. Even though they had access to medical files, they could find practically nothing. And most of what they could find was written in highly technical language, peppered with statistics and pharmaceutical names of medicines. "I couldn't find anything from a patient's point of view," said my neurologist's receptionist sadly. "Maybe you could write one. Maybe, I thought at the time. But where would I put it? Well, now I know."

Internet description 5: "My sisters went to the medical library and got the only information they had on SJS. No one should have to hunt for this information. It should be made readily available to all patients and families who experience this nightmare. We could only find one article."

Internet description 228: "...have also had great difficulty finding information on treatments as most doctors i have seen have never even heard of the syndrome."

Internet description 61: "Eventually I made a full recovery but was not given a clear reason why I had come down with SJS and if it was likely to re-occur, I found there was very little information available at the time and am still looking."

Internet description 119: "My daughter contracted SJS in August 2001, at the age of 3 years old. After many many months of searching to try and find another family that has had to experience and suffer this terrible disease in England, I have found no one.SJS seems to be extremely rare and hardly anybody(in the medical profession or otherwise) knows about this disease in England. There does not seem to be any support groups at all, there just seems to be a total lack of knowledge on this disease. Therefore to find this site is wonderful for my daughter and my family, at last I have found people who can totally understand what my daughter and my family has had to experience."

3.5 Discussion

3.5.1 Identification of internet narratives

The majority of narratives meeting my inclusion criteria were identified from two major support group websites, but only two were from personal blogs, and none were found on the social networking sites searched. There may be a few possible explanations for this. Many authors, for example, described how they felt they lacked information at the time of the event. They explained how this led them to undertake a general search of the internet for more information, leading to the discovery of the support group websites identified from the current study. It is possible therefore, that individuals coming across these websites during their search for more information, were more likely post their experiences here, than create their own personal blogs. In addition, the support group websites identified were publicly accessible through common internet search engines such as *Google,* whereas the social networking sites mentioned required the user to subscribe or register with the site; individuals may therefore have been less inclined to post on them. Finally, the groups on the social networking sites searched appeared to encourage individuals to 'join' with the aim of adding to membership numbers, rather than to share their experiences.

3.5.2 Descriptive analysis

Although almost two thirds of all internet descriptions were written by individuals who had directly experienced SJS/TEN themselves, the remaining narratives were posted by the relatives of patients. Almost two thirds of relative postings were made by parents (45/69), which in part, may be explained by a significant proportion of children affected by SJS in

our study. It was also apparent that a number of patients who had relatives post on the internet had either died from the condition, or were still acutely unwell and being treated for the condition. The majority of relative posters were female (48/69), and thirty of these were mothers of patients. It is not clear why such a gender imbalance exists, although this may be because mothers are more likely to be carers of children in acute illness than men (Maume 2008).

The majority of those who indicated their country of residence lived in the United States (US) or the United Kingdom (UK). This might be explained by the fact that the two main websites I identified containing the majority of narratives meeting my inclusion criteria, originated from the US (*www.sjsupport.org*) and the UK (*www.patient.co.uk*). In addition, I only selected websites and narratives written in English, and hence a greater proportion of authors were likely to originate from countries where English is spoken as the primary language, such as the US or UK. Finally, individuals would also be less likely to post their narratives on the internet if they were from countries where the internet is not as freely available as it is in the UK or US, although increasingly, very few such places exist now.

Around 82% of postings (170/208) mentioned or implied the likely cause of the reaction; of these, 89% (152/170) were believed by authors to be drug-related. The culprit drug was indicated in 89% (135/152) of drug-related cases. The majority of authors therefore appeared well informed, and were aware of the suspected drug cause. In some cases, it was not clear whether this suspicion was based on medical advice, or on the patient or relative making an association themselves. However, a comparison of the most common cited culprit drugs in our study with previous epidemiological studies examining SJS/TEN shows some congruity

(Roujeau et al. 1995) (See tables 2-1 and 3-2). Unsolicited patient descriptions of ADRs on the internet, such as those analysed in my current study, may therefore be of potential use in improving pharmacovigilance, as I will discuss later.

The majority of description authors (164/208) appeared to have posted on websites in a desire to share their experiences with others, and hence provide a source of support for others who had also experienced SJS/TEN. These findings are in keeping with previous research focusing on internet accounts of personal illness, which showed that whilst a number of accounts were primarily constructed to explain the illness and consequent emotional changes, other accounts were constructed to give advice and support to others (Hardey 2002).

Although altruism may be a key factor in people's decisions to post, sharing their experiences can also be of therapeutic benefit for those posting. Writing about important personal experiences in an emotional way has in fact been shown to result in improvements in mental and physical health (Baikie and Wilhelm 2005;Pennebaker 1997;Pennebaker and Seagal 1999).

It is evident from undertaking a word frequency analysis of internet descriptions, that authors recurrently used similar words to describe their experiences, and the effects of the ADR. Similar to my interview cohort of survivors, many of the descriptions of the ADR were very detailed and vivid, and the words frequently used to describe the ADR reflect this. Words most frequently used by authors to describe their skin reaction included 'blisters', 'burn', 'rash', 'swollen', 'scars', 'pain' and 'lesions. Other words frequently used in

narratives included ‘horrific’ and ‘devastating’, emphasising that the ADR was a traumatic event for many of the authors.

3.5.3 Qualitative analysis

The majority of themes found through interviewing survivors of SJS/TEN were also identified on analysis of the internet descriptions. These included aspects of their understanding of SJS/TEN (e.g. the rarity of the condition), their experiences of the condition (e.g. symptoms of the ADR being confused for another condition and their perception of healthcare professionals awareness for the condition), and the impact of the ADR on their current life (e.g. avoidance of medicines after the event). In contrast to my interviews with survivors however, the internet descriptions did not shed much light on patients’ beliefs regarding why the ADR may have occurred. It is unclear why this may be, but one explanation, is that patients were prompted to explore their beliefs and views about their experiences fully in the interviews.

It general, it can be concluded that internet narratives of the ADR may yield similar data to that found through interviewing survivors face to face. My analysis of such unsolicited web-based material has therefore allowed a triangulation of the findings from my previous interview-based study, where narratives of the ADR were solicited by the researcher. Taking this into consideration, it could be hypothesised that internet searches, which are easier to conduct than face-to-face interviews, could usefully guide patient-centred care where data from interview studies may be difficult to obtain, particularly for rare conditions.

At the time of undertaking the current study, few studies examined internet descriptions of illness, and none had triangulated their findings by comparison with another method (Dickerson et al 2006; Kim 2009; Kinnane & Milne 2010; Mo & Coulson 2008;Mo & Coulson 2010; Overberg et al 2010; Rozmovits & Ziebland 2004).

I also identified several new themes from my analysis of internet descriptions, which were not found through interviewing survivors. This may be due to the fact that only a small sample was available for interview in my previous study, whereas in the current study, a larger sample was available, allowing access to a greater number of descriptions of the ADR. In addition, many of the novel themes and subthemes identified, centred around the questions, concerns, and fears that patients and their relatives had regarding the ADR, and hence may not have been automatically elicited through my interviews with survivors, as these areas were not covered in detail in the interview topic guide.

Patients and their relatives directly sought advice from others regarding the condition and its complications, including whether the condition was hereditary and could be 'passed on' to their children. Patients and their relatives also described fears and concerns, based on information they received from healthcare professionals or through their own research. These included a fear of a recurrence of the condition, fears for the effects on pregnancy, and fears of future infertility.

Many of these fears appear to be justified. A number of case reports in the literature exist, for example, regarding patients who have experienced recurrent episodes of SJS/TEN. Although many of these cases were precipitated by infections with *Mycoplasma pneumoniae* and

Herpes Simplex virus (Daubeney and Scopes 1991;Davis et al. 2002), cases of recurrent drug-induced SJS or TEN have also been reported, usually as a consequence of repeated exposure to the offending drug, or due to exposure to another drug with cross-reactivity (e.g. cephalosporins and carbopenems) (Paquet, Jacob, Damas, & Pierard 2002). In addition, a study of 55 paediatric patients with SJS/TEN admitted to hospital over a 7 year period showed that 18% had a recurrence of SJS up to 7 years after the index episode, and 3 experienced multiple episodes. (Finkelstein et al. 2011). We also know that SJS and TEN can affect any mucous membrane including that of the reproductive tract. Although there is limited evidence in the literature regarding the effects of SJS and TEN on long-term fertility, vaginal adhesions and stenosis are known sequelae of SJS and TEN, and can result in complications during childbirth (Hart et al. 2002;Kratzert et al. 1988;Oplatek et al 2006;Wilson & Malinak 1988).

Patients and relatives also described other fears however, which I have interpreted as unsubstantiated. These include concerns that other conditions they subsequently developed (which are not known to be related to SJS or TEN), may have developed as a consequence of their previous experience of the ADR.

In summary, the findings described show that patients and relatives posting on the internet felt that they lacked information, and had many unanswered questions and concerns about the ADR after the event. It could be hypothesised, therefore, that communication with patients and their relatives could be improved, and that the concerns and queries raised in the internet descriptions analysed, could be used to guide healthcare professionals in improving their communication and management of those who have experienced the ADR.

One proposal might be that healthcare professionals actively address the topics related to these concerns with patients, or at least be aware that these concerns may exist, so that they might be addressed promptly should they arise. How this might be done practically, is discussed in Chapter 5.

Authors described complications such as severe visual impairment or blindness as a result of SJS/TEN, which did not feature significantly in the findings of my previous study of survivors. This may be because I was unable to recruit patients who were significantly visually impaired, as they were unable to read the recruitment literature sent out to them; a limitation I identified in my previous study. In addition, only a small sample of patients could be interviewed, and thus may not be representative of the SJS/TEN population as a whole.

Authors also described experiencing sexual dysfunction, which again, was not discussed in the interviews. This may again be due to the fact that the numbers interviewed were small, but another explanation is that individuals may feel uncomfortable discussing sensitive issues such as sexual dysfunction face to face with an interviewer, whereas they may be more comfortable putting it down in writing and posting anonymously on the internet.

Description authors described altruistic reasons for posting their experiences, and wished to 'raise awareness' of the ADR and the 'dangers of drugs' in the general public so that others might avoid a similar experience. In addition, similar to the findings from my interview-based study, many authors perceived a lack of awareness of the ADR amongst healthcare professionals, and described how the diagnosis of their ADR was delayed as a result.

Unsurprisingly, they therefore provided this as a rationale for wanting to improve awareness amongst healthcare professionals also.

As well as constituting an essential part of their narrative, authors indicated that they wished to inform others of the suspected drug cause of the ADR. As discussed earlier, of those internet descriptions where a drug cause was implied, around 89% mentioned the culprit drug by name. These findings therefore support the idea that many members of the public might be motivated to report ADRs on internet forums, and that such reports may be potentially useful in detecting new ADRs. As discussed in Chapter 1, patient reports can significantly contribute to pharmacovigilance in a number of ways. In particular, we know that under-reporting of ADRs is a significant problem (Hazell & Shakir 2006), and such patient reports could therefore provide useful additional information for healthcare professionals and the pharmaceutical industry. In addition, around two thirds of internet descriptions by relatives were made by parents; such information on ADRs in children would be particularly valuable since ADRs in children in particular are poorly reported (Anderson & Choonara 2010). Finally, patient descriptions of ADRs are often 'richer' and more detailed than reports from healthcare professional, and are more likely to describe the effects on patients' lives (Avery et al 2011).

The potential of using the internet as a source of patient reports has in fact recently been demonstrated by the setting up of a public group on the social networking site *Facebook*, focusing on ADRs. Use of this site showed that although the ADRs reported were not serious or unexpected, their causal relationship with the suspected drugs was strong (Knezevic et al. 2011).

Finally, description authors described how they attempted to make a diagnosis themselves when healthcare professionals struggled to determine the cause for their presentation; a few authors, for example, described reaching a diagnosis of SJS themselves, through their own research using medical textbooks. This is perhaps not entirely unsurprising, as self-diagnosis triggers the diagnostic hypothesis in 18% of consultations with general practitioners, and a few studies have shown that a number of conditions such as recurrent urinary tract infection, recurrent anterior uveitis, and schistosomiasis can all be self-diagnosed correctly (Goyder et al. 2009).

3.5.4 Limitations

As I only used the most commonly used search engines by public users to search the internet, there is a possibility that I may have missed data available through other less commonly used search providers. I also only searched four of the most popular social networking sites, and hence may have missed data from other, less popular sites. In addition, the search terms or keywords I used to search the internet for unsolicited descriptions of the ADR were limited; it is possible that some patients posting their experiences in a blog, may not have mentioned the ADR by name in their descriptions, and hence may not have been identified through my search.

I could not independently verify the internet data I analysed, as generally, there was no corroborative medical information available apart from that which was detailed in the internet descriptions. I therefore could not confirm whether the internet descriptions analysed were true, and whether authors who identified themselves as having personal experience of drug-induced SJS or TEN, did indeed do so. The themes that emerged from the current study however, did include the majority of those that I previously identified by directly interviewing patients with a confirmed diagnosis of the ADR. It is likely, therefore, that the experiences described and the views expressed were genuine.

The experiences and views expressed in the internet descriptions may of course be unrepresentative of the entire cohort of those who experienced SJS or TEN. A reporting bias, with elderly patients using the internet less frequently (Campbell 2005), must also be recognised. This may explain the large proportion of reports describing the ADR in younger patients. However this may also in part be explained by the fact that many of those who posted on websites were parents of children who had recently experienced the ADR. In

addition, we know that the mortality in SJS and TEN increases with age, which may explain why fewer elderly patients submitted reports (Bastuji-Garin et al 2000). Finally, as only internet descriptions in English were included in the study, a cultural bias may exist in the descriptions analysed.

3.5.5 Conclusions

Internet descriptions of those experiencing SJS and TEN provided a rich dataset of personal experience of ADRs. Despite the rarity of SJS and TEN, I identified a large number of internet descriptions of the ADR, emphasising the potential value of analysis of internet descriptions of patient experience in rare disorders such as SJS and TEN, where engagement with patients might otherwise be difficult.

Patients and relatives who experienced SJS or TEN posted on support group websites or blogs to share their experiences, provide support to other sufferers, and seek advice from others who had similar experiences. Internet descriptions indicated that patients and their relatives shared common questions and concerns regarding the ADR, often long after the event.

Several new themes which were not found through interviewing survivors were also identified from internet narratives, including common questions and concerns shared by patients and relatives. My findings could be therefore be used to guide healthcare professionals in the management of patients who have experienced the condition and also in communicating with their relatives more effectively. In particular, healthcare professionals should be aware of these concerns so that they might be anticipated and addressed in future patients with the ADR.

4 CHAPTER 4–THE EXPERIENCE OF ADVERSE DRUG REACTIONS IN THE VERY ELDERLY AND THEIR IMPACT ON MANAGING HYPERTENSION

I have published a paper related to this chapter**:** Butt TF, Branch RL, Beesley L, Martin U. Managing hypertension in the very elderly: effect of adverse drug reactions (ADRs) on achieving targets. *Journal of Human Hypertension* 2010; 24**,** 514-518. (See Appendices)

4.1 Introduction

The population in the UK is ageing. In 1981, just 1% of the population was aged 85 years and over, but in the last 25 years, the number has doubled to 1.2 million and is expected to further increase to 2.9 million by 2031. Four per cent of the UK population will then be 85 years or more (Dunnell 2007). The increase in life expectancy over the past century has been brought about by improvements in sanitation, better housing, improved healthcare including immunisation programmes, and also improved medical treatments.

The projected doubling of the population aged 85 years over the next 25 years will have major implications for the provision of healthcare to this very elderly group. As the population ages, more people are expected to develop chronic age-related conditions such as hypertension. At present, it is estimated that more than 50% of the 12 million people in the UK over 60 years are hypertensive, even when a relatively high threshold (blood pressure ≥160/95 mmHg), is used for diagnosis (Williams et al. 2004).

Several characteristics of ageing including age-related impairment of drug metabolism, enhanced pharmacodynamic sensitivity to specific drugs, reduced physiological reserve and

homeostasis, cognitive impairment, an increased number of comorbidities, and multiple medications, all render prescribing in the elderly a challenging and complex process and increase the risk of ADRs.

4.1.1 Predisposing factors for ADRs in the elderly

Many studies have neglected the issue of whether the increased risk of ADRs in the elderly is attributable to age alone or to the fact that the elderly are more likely to have several other co-existing conditions for which they may be taking multiple medications, thus increasing the risk of ADRs (Routledge et al. 2004).

A review of the literature undertaken by Gurwitz and Avorn (1991) found that studies often combined data for all drug exposures for each patient and reported the risk for any ADR, thus providing little useful information about the risks associated with individual drug therapies. Also, as elderly patients may be taking multiple medications, it is may be difficult to determine which individual drug is responsible for a particular ADR.

Although the association between age and the risk of ADRs would be best determined through an analysis of the effects of individual drugs, this is often not possible as many clinical trials of individual drugs have excluded older patients altogether, and many studies that have included elderly patients failed to control for important clinical differences to distinguish the independent effects of age (Gurwitz and Avorn 1991).

One prospective randomised study of hospital inpatients showed that the incidence of preventable ADRs increased with the patients' age and resulted in a longer inpatient stay as compared to those that were non-preventable (Gholami and Shalviri 1999).

Other studies have found an association between advanced age and ADRs in patients with specific conditions only. Dormann et al (2001) for example, found that although there was an association between advanced age and ADRs in patients with biliary disease, this association was lost when analysing patients with gastroenterological disease overall (Dormann et al. 2001).

Most ADRs in the elderly are dose-related, in that the ADR is an 'accentuation' of the known pharmacological effect of the drug, and thus predictable and potentially avoidable. A post-hoc analysis of inpatients showed that the ADRs experienced by the elderly tend to be more severe and less likely to be idiosyncratic (Bowman et al. 1996).
I will now discuss predisposing factors that have been identified for ADRs in the elderly.

4.1.1.1 Polypharmacy

Polypharmacy can be defined in many different ways, and definitions vary according to the patient population and study setting. Although some have defined it as: 'the use of medications that are not clinically indicated', in practice, polypharmacy can be defined as: 'using more than a certain number of drugs, irrespective of the appropriateness of their use' (Masoodi 2008).

Both polypharmacy and long duration of therapy, are characteristic of drug therapy in the elderly. Drugs prescribed in the elderly are commonly for chronic conditions and hence are often continued long-term. Studies examining the frequency of medicines prescribed for older people in the community, have found that the commonest drugs prescribed include diuretics, followed by analgesics, hypnotics, sedatives, drugs for rheumatological disorders, and beta-adrenoceptor antagonists. A rise in the use of cardiovascular drugs in the elderly has also been noted, as well as an overall increase in the use of prescription medicines, and over- the counter medications (Goh et al. 2009;Martin and Coleman 2007).

Numerous studies have confirmed a positive correlation between polypharmacy and the incidence of ADRs in the elderly (Macedo et al. 2011;Mannesse et al. 1997;Nguyen et al. 2002;Olivier et al. 2009;Veehof, Stewart, Meyboom-de Jong, & Haaijer-Ruskamp 1999). In addition, a review of the epidemiology of serious ADRs in the elderly concluded that the most important determinant of risk for ADR-related hospital admission is the number of drugs being taken concurrently (Atkin et al. 1999).

Commonly occurring ADRs found to be associated with polypharmacy include falls (due for example, to orthostatic hypotension caused by diuretics or sedation) and gastrointestinal ADRs including haemorrhage (Mannesse et al. 1997; Veehof et al. 1999).

Justifiably, there are several reasons for polypharmacy in the elderly. As discussed previously, many diseases requiring medication are age-related, and several may co-exist in the same patient. In addition, it may not be possible to achieve an adequate therapeutic response from the use of a single drug, and this is particularly true for conditions such as

hypertension. Finally, there is also an increasing promotion of therapeutic regimens including two or more drugs used in combination for the optimum management of other conditions, such as heart failure, ischaemic heart disease, and diabetes mellitus (Martin & Coleman 2007).

The elderly, however, are at risk of a phenomenon known as the 'Prescribing cascade', which begins when an ADR to a prescribed drug is misinterpreted as a new medical condition. Another drug is then prescribed for the symptoms of the ADR, and as a result, the patient is put at risk of developing additional adverse effects related to the potentially unnecessary treatment (Rochon and Gurwitz 1997).

Drug interactions are one mechanism by which polypharmacy can increase the risk of ADRs. A change in either the magnitude or duration of action of one drug, caused by the presence of the second may occur. This may enhance or reduce the efficacy of either drug, or a new effect may be seen, which does not occur with either of the drugs alone. In addition, the prevalence of drug interactions increases in a linear mode with increasing age and with the number of drugs prescribed (Lin et al. 2011).

Several types of interaction are known to exist: drug-drug, drug-disease (e.g. calcium channel blockers such as verapamil in patients with congestive heart failure), drug-food (e.g. calcium channel blockers such as nifedipine and grapefruit juice), drug-alcohol (e.g. warfarin and alcohol), drug-herbal products (e.g. warfarin and St. John's Wort), and drug-nutritional status (e.g. malnutrition resulting in low plasma albumin, causing an increased toxicity with protein bound drugs). Drug-disease or drug-patient interactions occur when a drug has the

potential to exacerbate an underlying disease or medical disorder (Lindblad et al. 2006;Mallet et al. 2007;Pickering 2004).

4.1.1.2 Altered pharmacokinetics

Elderly patients may develop drug-related problems even when the medication is confined to a single drug, due to pharmacokinetic and pharmacodynamic changes associated with ageing.

Firstly, the volume of distribution of drugs may be affected; with increasing age, there is a decrease in total body water, and a corresponding increase of up to 20 to 40% in adipose tissue in relation to total body weight. Lipid soluble drugs such as diazepam, for example, will therefore have a larger volume of distribution in the elderly and may have a prolonged action due to the longer elimination half-life, with an increase risk of associated adverse effects, such as drowsiness and falls (Aymanns et al. 2010;Martin & Coleman 2007).

Secondly, ageing can affect drug absorption and bioavailability. Old age is associated with slowing of gastric emptying, decreased peristalsis, and slowing of colonic transit, largely secondary to region-specific loss of neurons, and this may affect drug absorption (Mclean and Le Couteur 2004). In addition, serum albumin levels may decline with age; this may be related to disease states (e.g. proteinuria in renal disease), immobility, and poor nutrition, all of which are more prevalent in the elderly. Reduced albumin levels may result in a reduction in the protein binding of drugs such as phenytoin, and hence an increase in free drug concentrations in the plasma, with a potential increase in the risk of ADRs (Martin & Coleman 2007).

Thirdly, metabolism and hepatic clearance of drugs may also be impaired in the elderly, predisposing to ADRs. For example, liver size and hepatic blood flow are diminished by 25-35% in the elderly, along with a decrease in bile flow. This, in combination with a decreased specific content of cytochrome P450 enzymes, may result in a decrease in hepatic clearance of drugs in the elderly (Ginsberg et al. 2005). Despite these changes however, hepatic function is generally well maintained in the elderly and few clinically significant alterations in drug metabolism occur.

Ageing is also associated with some reduction in first pass metabolism, and hence, the bioavailability of a few drugs may also be increased (Shi and Klotz 2011). The administration of nifedipine in the elderly for example, is associated with a reduction in first pass metabolism and clearance compared to younger patients. This results in higher and more prolonged plasma concentrations, which in turn may cause an increased hypotensive effect and adverse events associated with it (Robertson et al 1988). This decrease in clearance also explains the greater reductions in blood pressure usually seen in older compared to younger patients receiving the same doses (Schwartz 1996).

Finally, and most importantly, there is a steady decline in renal function and glomerular filtration rate (GFR) as part of the ageing process. In fact, in people aged 65 years and over, pharmacokinetics are influenced more by the loss of kidney function than by the ageing process of any other organ. The average age-related loss in GFR is reported as 0.4 to 1.02 ml/min per year, and a GFR of 60 ml/min, suggestive of stage 3 kidney disease, is observed in 15-30% of elderly people (Aymanns et al. 2010).

This decline in renal function is thought to be secondary to a reduction in the total number of glomeruli, increased sclerosis in the remaining glomeruli, and altered renal tubular function (Aymanns et al. 2010). The ability of the kidney to concentrate urine maximally after water deprivation is decreased as a result, and may, for example, increase the risk of dehydration with diuretic therapy. Finally, advanced age is associated with the increased incidence of conditions such as hypertension, vascular disease, and diabetes; these clearly may impact on renal function independent of primary ageing biology, predominantly through arteriosclerosis (Mclean & Le Couteur 2004).

Renal elimination of drugs and water soluble drug metabolites may therefore be reduced in the elderly due to the age-related decline in renal function. Drugs and drug metabolites which are eliminated by the kidneys can accumulate as a result and cause toxicity in the elderly particularly if they are given at the standard doses, as is the case, for example, with digoxin and morphine.

This has important clinical implications. Data from over eleven thousand elderly hospitalised patients showed that those with evidence of renal impairment had an increased risk of developing ADRs. A high proportion of elderly patients had 'concealed' renal impairment (i.e. normal serum creatinine levels but reduced estimated GFRs), and were at a similar increased risk of ADRs as compared to those with overt renal impairment (i.e. those with increased serum creatinine levels and reduced estimated GFRs) (Corsonello et al. 2005).

Of relevance to my current study, a decrease in renal function via the mechanisms described can cause a number of complications specifically from antihypertensive therapy. The adverse

effects experienced are dependent on the antihypertensive agent used, and include malaise, excessive falls in blood pressure, postural hypotension, water and electrolyte disorders, renal impairment, and neuropsychological disturbances. Diuretics, for example, should be used with caution in the elderly to avoid hyponatraemia, hypotension, and dehydration (Muhlberg and Platt 1999).

Many drugs including antihypertensives such as diuretics and ACE-inhibitors may also themselves adversely affect renal function in the elderly. Such drug-induced kidney injury is commoner in those aged 65 years and above, and occurs through a number of different mechanisms including vasoconstriction, inhibition of the renin-angiotensin-aldosterone system, and acute tubular necrosis (Rajakaruna and Butt 2007).

In conclusion, dose adjustment of renally eliminated drugs may therefore be necessary in older people.

4.1.1.3 Altered pharmacodynamics

The elderly may show either an increased or decreased responsiveness or sensitivity to drugs. In some cases, the increased responsiveness to a drug may be explained by changes at receptor and cellular level, or age-related impairment of homeostatic mechanisms. An inter-play with changes in pharmacokinetics (e.g. reduced clearance) may also occur (Martin & Coleman 2007). Hence, with the same drug concentration at the site of action, significant differences in the response to various drugs have been observed in the elderly when compared to younger patients (Trifiro and Spina 2011).

Advanced age can affect the activity and expression of many receptors, and this is particular relevant for antihypertensive agents. One example is the down-regulation of beta-adrenergic receptors, and the reduced cyclic AMP (cAMP) response to beta-adrenergic stimulation. This may explain why beta-adrenoceptor blockers may be less effective in treating hypertension in the elderly than other antihypertensives (Mclean & Le Couteur 2004). On the other hand, altered homeostasis makes elderly patients more susceptible to postural hypotension with beta-adrenoceptor blockers. Likewise, verapamil is less likely to cause PR interval prolongation in the elderly as compared to younger patients because of decreased sensitivity to calcium channel blockade in the conducting system of the heart. However the net effects of any given dose may be maintained as the clearance of verapamil is reduced in the elderly leading to cardiac toxicity (Mclean & Le Couteur 2004).

Altered homeostatic mechanisms due to impaired baroceptor function, may contribute to the greater reduction of blood pressure in the elderly with antihypertensives, as discussed for beta-adrenoceptor blockers. In younger patients, any fall in blood pressure usually leads to a compensatory tachycardia, partly offsetting the fall in cardiac output. This compensatory response is diminished in the elderly however, and may cause orthostatic or postural hypotension as a result (Martin & Coleman 2007). Calcium channel blockers for example, have been shown to result in greater reductions in blood pressure in older compared to younger patients receiving the same doses. The dosage required to reduce blood pressure to a target level is often lower in older patients, and as well as a reduced clearance of these drugs, impaired homeostatic mechanisms are no doubt a major contributor. (Schwartz 1996)

The increased sensitivity of the elderly to the effects of other drugs such as benzodiazepines is also well recognised. This is thought to be due to a combination of altered tissue sensitivity, different rates of entry of the drug into the tissues of the central nervous system, as well as increased volume of distribution in the elderly as previously described. The half maximal effective concentration (EC_{50}) for sedation from intravenous midazolam for example, is reduced by 50% in older people, despite the absence of significant age-related pharmacokinetic differences (Albrecht et al. 1999). A review of studies undertaken looking at the adverse effects from benzodiazepine use in the elderly has shown that they are at an increased risk of falls, drowsiness, confusion, and related central nervous system antidepressant effects (Greenblatt et al. 1989).

4.1.1.4 Inappropriate prescribing

Inappropriate prescribing is thought to be a major cause of ADRs in elderly patients, and describes the use of medicines that pose more risk than benefit, particularly where safer alternatives exist. It also includes the misuse of medicines (e.g. prescribing a drug at the wrong dose or duration), the prescription of medicines with clinically significant drug-drug and drug-disease interactions, and importantly, the under-use of potentially beneficial medicines (Hamilton et al. 2009).

Appropriateness of prescribing can be assessed by process or outcome measures that are explicit (criterion-based) or implicit (judgement-based). Process measures assess whether the prescription is in accordance with accepted standards, whereas outcome measures are indicators of adverse outcomes (e.g. ADRs, hospital admissions etc). Explicit indicators are usually developed from published reviews, expert opinions, and consensus techniques,

whereas in implicit approaches, the clinician utilise clinical information from the patient to make judgements (Spinewine et al. 2007).

Explicit criteria to identify potentially inappropriate medications (PIMs) include those proposed by Beers et al (1991). These were formulated by obtaining expert consensus using a modified Delphi method; a set of procedures and methods for formulating a group judgement for subject matter (such as prescribing in the elderly), where precise information is lacking (Beers et al. 1991). These criteria, now known as the Beers' criteria (BC), were updated in 2003, and covered two groups of medications: i) medications or medication classes that should be generally avoided in people aged 65 years and above, because they are either ineffective or they pose an unnecessarily high risk for the elderly and safer alternatives are available, and ii) medications that should not be used in older people known to have specific medical conditions. The study identified forty-eight individual drugs or drug classes to avoid in older adults and twenty diseases and medications to be avoided in older adults with these conditions. Of these, sixty-six were considered by the panel to have adverse outcomes of high severity, including non-steroidal anti-inflammatory drugs such as indomethacin, benzodiazepines, and amiodarone (Fick et al. 2003).

The evidence to support the hypothesis that inappropriate medications based on the Beers' Criteria are associated with an increased risk of ADRs in the elderly is, however, debatable. Although a few studies have found that BC medications are associated with an increased risk of adverse events and mortality (Chang et al. 2005;Lau et al. 2005;Perri et al. 2005), many others have found the contrary (Budnitz et al. 2007;Laroche et al. 2007;Page and Ruscin 2006;Shiyanbola and Farris 2010).

In addition to insufficient evidence to support an association between the prescribing of inappropriate drugs (such as those identified by the Beers' Criteria) and adverse events, there are disadvantages in using lists of 'drugs to avoid' as a sole measure for inappropriate prescribing in the elderly. Firstly, this approach may identify appropriate prescribing as inappropriate, as it does not take into consideration the context of prescribing in particular patients (i.e. poor specificity). Secondly, this approach does not include other categories of poor prescribing such as the omission of or under-use of medicines (e.g. failure to prescribe warfarin in older patients with chronic atrial fibrillation who are at high risk for arterial embolism), lack of medication monitoring, prescription duplication, or drug-disease interactions (Spinewine et al. 2007).

Examples of implicit or judgement-based measures of inappropriate prescribing include the Medication Appropriateness index (MAI). This index assesses ten elements of prescribing: indication, effectiveness, dose, correct directions for use, whether the directions are practical, drug-drug interactions, drug-disease interactions, unnecessary duplication with other drugs, acceptable duration of therapy, and cost-effectiveness of the drug (Hanlon et al. 1992). Although the MAI has good intra-rater and inter-rater reliability, and has face and content validity, it can be time consuming to implement, and like the Beers' Criteria, does not assess under-prescribing.

Spinewine et al (2007) critically reviewed studies that measured one or more appropriate prescribing process measure (including measures such as the Beers' Criteria and MAI), and found that most measures of appropriateness relied exclusively on drug data and did not extend beyond pharmacological appropriateness. As a result, they concluded that many

measures were inadequate, and failed to take into account the perspectives of patients and prescribers.

It is clear, therefore, that as adequate measures of inappropriate prescribing have been lacking, a definitive link between inappropriate prescribing and the increased risk of ADRs has been difficult to prove.

New criteria, known as the Screening Tool of Older persons' Prescriptions (STOPP) and Screening to Alert Doctors to Right Treatment (START) however, were recently devised and validated to overcome many of the shortcomings described above (Gallagher et al. 2008). The STOPP criteria, validated using a Delphi Consensus technique, consist of 65 clinically significant criteria for potentially inappropriate prescribing in older people, with each criterion accompanied by an explanation as to why the prescribing practice is potentially inappropriate, whereas START consists of 22 evidence-based prescribing indicators for commonly encountered diseases in older people. Specifically for drugs used to treat hypertension in the elderly, STOPP identifies for example, using a loop diuretic as first-line monotherapy for hypertension in the elderly, as potentially inappropriate, as safer and more effective alternatives exist. Other potentially inappropriate drugs which would not have been identified by the Beers' Criteria include using a thiazide diuretic in an elderly patient with a history of gout, or alpha-adrenergic blockers specifically in males with frequent urinary incontinence.

The START criteria identify indicated treatments which should be considered in those aged 65 years and above, as long as no contraindication exists. Relevant to my current study,

these include the prescribing of antihypertensive therapy where the systolic blood pressure is consistently above 160 mm Hg.

The authors of the STOPP/START criteria also showed that the STOPP criteria detect ADRs that are causal or contributory to hospital admissions in older people 2.8 times more frequently than Beers' criteria (O'Mahony et al. 2010). In addition, the application of the STOP/START criteria has been shown in a recent randomised controlled trial to result in significant and sustained improvements in prescribing appropriateness, in terms of reducing the use of unnecessary medicines and associated potential drug-drug and drug-disease interactions, with a reduction in the under-utilisation of indicated drugs (Gallagher et al. 2011). Finally, a recent prospective study of 600 consecutive patients aged 65 years or older admitted to hospital, showed that PIMs identified by STOPP criteria were significantly associated with avoidable ADRs in older people that caused or contributed to urgent hospitalisation, whereas the prescribing of Beers' Criteria PIMs were not (Hamilton et al. 2011).

4.1.2 ADRs to antihypertensive drugs in the elderly

A number of studies have shown that antihypertensive agents are amongst the drugs most frequently known to cause ADRs in the elderly. The Italian Group of Pharmacoepidemiology in the Elderly (GIFA) study, a multicentre survey conducted over a ten-year period, for example, found that antihypertensive agents such as diuretics and calcium channel blockers**,** both first line agents in treating hypertension in the elderly (Williams et al. 2004), were the commonest causes of ADRs in the elderly (Onder et al. 2002).

Similarly, a population-based cross-sectional study involving 2143 elderly residents in Brazil, found that antihypertensives were the commonest causes of potential drug-drug interactions (PDDIs). Treatment combinations of an angiotensin-converting enzyme (ACE) inhibitor with a thiazide or loop diuretic (associated with hypotension) was the most frequent cause of PDDIs, followed by PDDIs between both ACE inhibitors and thiazide diuretics, and NSAIDs (renal dysfunction, electrolyte imbalance, and hypotension). The study also showed that the risk of a PDDI was significantly increased among elderly individuals using six or more medications, and in patients with hypertension. The study however, only identified potential interactions rather than actual interactions that occurred (Secoli et al. 2010).

Other studies have focused on the use of individual antihypertensive agents in the elderly, reporting on tolerability as well as efficacy. One study, for example, found that the beta-adrenoceptor blocker bisoprolol had a similar hypotensive efficacy in the elderly as in younger patients, and that there were no significant differences in ADRs between the groups. However the numbers of patients participating in the study were small (forty patients aged

below 65 years vs. twenty aged over 65 years) (Broncel et al. 1998). A larger study of 2012 patients with mild to moderate hypertension who received 5-10 mg of bisoprolol showed that 11.6% reported adverse effects such as vertigo, fatigue, gastrointestinal disturbances, and headache, but that the incidence of adverse effects was not greater in those aged 60 years and above, and was infact highest in the age group 31-40 years (Hoffler and Morgenstern 1990). This apparent lower incidence of ADRs with beta-adrenoceptor in the elderly may possibly be explained by the down-regulation of beta-adrenergic receptors in this age group as previously discussed.

Thiazide diuretics on the other hand, commonly cause metabolic adverse reactions in the elderly, including hypokalaemia, hyponatraemia, and renal failure, although using a reduced dose in hypertension may reduce these adverse effects (Baglin et al. 1995).

ACE inhibitors are effective in elderly patients with hypertension, despite the fact that plasma renin activity is lower than in younger individuals. This may be due to decreased renal clearance of the drug, but these altered pharmacokinetics, combined with impairment of cardiovascular reflexes, render elderly patients more susceptible to first-dose hypotension with this class of drug (Tomlinson 1996). Other adverse effects reported with ACE inhibitors in the elderly include headache, flushing, and dizziness (Puig et al. 2007).

Calcium channel blockers are generally well tolerated in the elderly, but are also not without adverse effects. The commonest ADRs reported include ankle oedema, headache, and flushing, although some calcium channel blockers, for example, lercanidipine, appear to be better tolerated in the elderly as compared to others (Beckey et al. 2007;Cherubini et al. 2003). Low dose combinations of antihypertensives have also been shown to be associated

with a lower incidence of ADRs in the elderly when compared with higher doses of drugs used singly, and in some studies, have been shown to have an adverse effect profile similar to placebo (Leosco et al. 2002;Morgan et al. 1992;Prisant 2002).

Centrally acting agents such as moxonidine have also been shown to be generally well tolerated in the elderly, although ADRs experienced include nausea and fatigue (Martin et al. 2005).

Finally antihypertensives involved in direct renin inhibition (e.g aliskiren) or aldosterone blockade (e.g. eplenerone or spironolactone) are also generally well tolerated in the elderly, although reported ADRs include headache and hyperkalaemia respectively (Basile 2009).

The Hypertension Detection and Follow-up Program formed one of the largest groups to date, on which detailed community surveillance of long-term antihypertensive therapy and its adverse effects was undertaken in individuals aged 60–69 years in the United States. Definite or probable ADRs severe enough to cause discontinuation of the treatment were reported in 9.3% of over 5000 participants, and an additional 23.4% had treatment discontinued due to possible ADRs. The five-year incidence of total ADRs was 29.8%; however less than 1% required hospitalisation for serious adverse effects (Curb et al. 1985).

Perceived ADRs to antihypertensives are also associated with non-adherence to treatment (Lowry et al. 2005;Mino-Leon et al. 2007) which may significantly contribute to inadequate blood pressure control (Elliott 2008).

In summary, it is clear that ADRs to antihypertensive agents are a significant problem. As well as affecting quality of life, they may result in discontinuation of treatment, limit treatment options, reduce adherence to therapy, and result in inadequate blood pressure control.

4.1.3 Treating hypertension in the elderly

The evidence base for prescribing in older people in general is unfortunately small and clearly disproportionate to the amount of prescribing occurring in this age group. In the year 2000, only 3.45% of 8954 randomised controlled trials and 1.2% of meta-analyses were for patients over the age of 65 years (Nair 2002). It is clear that the elderly have been poorly represented in clinical trials, and hypertension trials are no exception. This is surprising given the fact that hypertension is more prevalent in the elderly.

As many hypertension trials in the past have excluded the very elderly (i.e. those aged 80 years and above) it has been unclear whether the treatment of such patients conferred more benefit than risk. In addition, many hypertension studies that have recruited elderly patients may have included too few patients to show benefit of treatment. It is unsurprising, therefore, that the results of many of these studies are not consistent. Some studies, for example, have shown that actively treating hypertension in the elderly may be associated with a reduction in cardiovascular mortality, but not in overall mortality.

The European Working Party on high blood pressure in the elderly trial is one example, and is one of earliest double-blind placebo controlled trials of antihypertensive treatment in the elderly (Amery et al. 1985). Eight hundred and forty hypertensive patients aged over 60 years were randomised to receive either active treatment (hydrochlorothiazide and triamterene) or matching placebo. Cardiovascular mortality was reduced in the actively treated group by 38%, a non significant decrease in cerebrovascular disease, but no significant difference in all cause mortality between the two groups.

A number of other studies however, showed that lower systolic blood pressures may infact be paradoxically associated with increased mortality in the elderly (Boshuizen et al. 1998;Langer et al. 1989;Mattila et al. 1988;Oates et al. 2007;Satish et al. 2001;Taylor et al. 1991). Mattila et al (1988) analysed the 5 year survival rates of 561 elderly people in Finland, 83% of whom were aged 85 years or more. Those included in the study were either residing in the community or nursing homes, or were patients in hospital. Participants were divided into six groups based on blood pressure. The greatest mortality was observed in those in the lowest systolic and diastolic groups (e.g. < 120 mm Hg systolic and 70 mm Hg diastolic) and least in those with systolic pressures of 160 mm Hg and diastolic pressures of 90 mm Hg or more. Another Finnish study of 2270 patients aged 65 years and above showed that in men aged 75 years and above, low diastolic blood pressures were associated with the greatest 'all cause' and cardiovascular mortality, and higher diastolic blood pressures predicted survival (Langer et al 1989).

It is likely, however, that comorbidities may have been confounding variables in the studies above as they were not adjusted for. Hence, the apparent inverse association between blood

pressure and mortality may be explained by the fact that ill health (for example, due to cardiac causes), may result in very low blood pressure, and may have contributed to the increased mortality found in this group.

This problem may have been partly addressed by other studies subsequently performed in the 1990s, which excluded elderly hypertensive patients with comorbidities such as ischaemic heart disease (including previous myocardial infarction), stroke, orthostatic hypotension, and other severe illnesses. The Swedish Trial in Old Patients with Hypertension (STOP-Hypertension) was one such prospective placebo controlled study of elderly hypertensives aged 70-84 years. 1627 patients were recruited, of whom half were allocated to active treatment with a beta-adrenoceptor blocker alone or in addition to a diuretic, and half to placebo. Compared to placebo, the study found that active treatment not only significantly reduced the primary endpoints of stroke morbidity and mortality, the rate of all cause mortality was also significantly reduced (Dahlof et al. 1991).

Other trials, such as the Systolic Hypertension in Europe (Syst-Eur) trial (Staessen et al. 1997b) and the Systolic Hypertension in the elderly Program (SHEP) (SHEP cooperative Research Group 1991) also found that active treatment was associated with lower rates of cardiovascular mortality, although overall mortality was not influenced.

A subsequent subgroup meta-analysis of randomised controlled trials of antihypertensive drug use in patients aged 80 years and above, however suggested that although treatment of hypertension in this group resulted in a 36% reduction in stroke, this was offset by an increased risk of death from any cause (Gueyffier et al. 1999).

4.1.4 HYVET

It is clear that the evidence for treating hypertension in the very elderly in the past has been inconclusive, but as discussed, this is likely to be due to the fact that small numbers were recruited to these trials.

The Hypertension in the Very Elderly trial (HYVET) in 2008, however, recruited a much larger sample of almost 4000 elderly patients, overcoming previous problems related to small sample sizes, and the results of this study has subsequently led to a re-evaluation of the clinical management of hypertension in these patients (Beckett et al. 2008). This was a double-blind, placebo controlled trial performed in 195 centres, in thirteen countries in Western and Eastern Europe, China, Australasia, and North Africa. 3845 patients aged 80 years and above, with a sustained threshold systolic blood pressure of ≥160 mmHg were randomly assigned to receive indapamide (sustained release 1.5 mg, with or without perindopril) or placebo, to achieve a target blood pressure of 150/80 mmHg. Treatment was associated with a 30% reduction in fatal or non-fatal stroke (95% confidence interval (CI) -1 to 50, p=0.06), a 23% reduction in the rate of death from cardiovascular disease (95% CI, -1 to 40, P=0.06), a 64% reduction in the rate of heart failure (95% CI, 42 to 78, P,0.001), and contrary to previous studies, a 21% reduction in the mortality rate from any cause (95% CI, 4 to 35, p=0.02).

The results of HYVET therefore indicate that treating hypertension to a target of 150/80 mm Hg with antihypertensive treatment based on indapamide, with or without perindopril, significantly reduces the risk of death from stroke and death from any cause in elderly patients. Interestingly, there were also fewer reported adverse events in the treatment group.

The number of serious adverse events reported was 448 in the placebo group but only 358 in the active treatment group, and only two in the active treatment group were classified as possibly being due to the trial medication. However, any minor ADRs experienced by patients were not reported in their findings.

As a result of the findings of HYVET, recent new guidance on the management of hypertension published by the National Institute of Clinical Excellence (NICE), recommends that hypertensive patients aged 80 years and above should be offered the same treatment as those aged 55 to 80 years (NICE 2011).

4.1.5 The role of ambulatory blood pressure monitoring in the elderly

Ambulatory blood pressure monitoring (ABPM) is a fully automated technique in which multiple blood pressure measurements are taken at regular intervals (usually every 30 minutes) over a 24–48 hour period, providing continuous blood pressure recording during patients' normal daily activities. At the end of the recording period, the readings are downloaded onto a computer. ABPM can provide information of the mean blood pressure over a 24 hour period, the diurnal pattern of blood pressure, and the variability in blood pressure. It therefore more accurately and reliably measures blood pressure than conventional office blood pressure measurements (i.e. blood pressure measurements taken using a conventional cuff device in the physician's office or healthcare setting) (Chavanu et al. 2008).

In older untreated patients with isolated systolic hypertension, ambulatory systolic blood pressure has been shown to be a significant predictor of cardiovascular risk over and above conventional blood pressure measurements (Staessen et al. 1999).

In addition, the adjustment of antihypertensive treatment based on ABPM monitoring instead of conventional office blood pressure measurements has been shown to lead to less intensive drug treatment with preservation of blood pressure control (Staessen et al. 1997a). This is likely to be due to the fact that on average, office measured blood pressure using a conventional cuff, is higher than mean blood pressure readings obtained using ABPM. The main reason for higher office blood pressure readings is the influence of the 'white-coat effect' or 'white coat hypertension' in the healthcare setting (see 4.1.6).

The elderly also have a greater variability in blood pressure compared to younger subjects, which is better detected through 24 hour ABPM (Drayer et al. 1982).

ABPM may therefore be very useful in the management of hypertension in the very elderly, and is thus the method of blood pressure measurement in my current study.

The diagnostic thresholds and treatment targets for hypertension in the majority of hypertension trials including HYVET were based on conventional office blood pressure measurements. An adjustment should therefore be made to the mean ABPM readings (to allow for the differences in home and office readings). At the time of undertaking my current study, this was an adjustment upward of 10 mmHg systolic and 5 mmHg diastolic in accordance with British Hypertension Society (BHS) Guidelines (Williams et al 2004). It

should be noted however, that these guidelines have recently been superseded by new NICE guidance (2011), which recommends making an upward adjustment to mean ABPM readings of 5 mm Hg systolic and 5 mm Hg diastolic for ABPM readings below 160/100 mm Hg, and an adjustment of 10 mm Hg systolic and 5 mm Hg diastolic for ABPM readings above 160/100 mm Hg.

4.1.6 White coat hypertension

White coat hypertension (also referred to as 'office hypertension') is a term used to denote individuals who have blood pressures that are higher than normal in the medical environment (reaching thresholds diagnostic for hypertension), but whose blood pressures are normal when they are going about their usual daily activities (Verdecchia et al. 2002). Mancia et al (1983) quantified the exact transient rise in blood pressure that occurs in the presence of a doctor as 4 to 75 mm Hg for systolic blood pressure and 1 to 36 mm Hg for diastolic blood pressure. This transient rise in blood pressure or 'white coat effect' may result in a marked over-estimation of blood pressure in many individuals. This effect, for example, may lead to either to a misdiagnosis of essential hypertension in un-medicated patients, or in individuals with reasonably well controlled blood pressure on treatment, a diagnosis of poorly controlled blood pressure, and as a consequence, inappropriate treatment (Mancia et al. 1983).

Although white coat hypertension is a consequence of the white coat effect, they are both separate entities, as the first is a binary (yes/no) definition, and the second is a quantitative measure of the blood pressure rise from before to during the clinic visit.

Verdecchia et al (2002) define white coat hypertension as being present if the conventional (office) blood pressure is persistently equal to or greater than 140/90 mm Hg with an average daytime ambulatory daytime blood pressure reading below 135 mm Hg.

Interestingly, the reverse of white coat hypertension (known as 'Masked hypertension' or 'Reverse White Coat Hypertension') may also be seen in older hypertensives, where mean ambulatory readings are higher than office readings. Although a lower proportion of the elderly show evidence for this phenomenon compared to white coat hypertension, it again emphasises the usefulness of ABPM in the elderly, not only to help avoid overtreatment in those with typical 'white coat hypertension' but also for ensuring adequate treatment is given to those with the reverse of this phenomenon (Wing et al. 2002).

4.1.7 Rationale for current study

Although the findings of HYVET support the hypothesis that treatment of hypertension should include the very elderly at least to a target blood pressure of 150/80 mmHg, based on what we know regarding the increased susceptibility of elderly patients to ADRs (and in particular, antihypertensives), it could be hypothesised that ADRs in the elderly may make treating blood pressure to such a target as proposed by HYVET, difficult to achieve in clinical practice. The aim of my current study therefore, was to determine whether the occurrence or potential risk of ADRs to antihypertensive drugs in the very elderly, limit the prescribing clinician's ability to follow the recommendations made by the HYVET study, in order to achieve blood pressure targets using ABPM in the secondary care setting.

4.2 Aims

1. To identify the proportion of patients aged 80 years and above referred to our secondary care hypertension service over a ten year period, and categorise them based on their 24-hour ambulatory blood pressure monitoring (ABPM) readings, according to the thresholds and targets used in the HYVET study.

2. To identify ADRs due to antihypertensive therapy experienced by patients referred.

3. To assess the impact of these ADRs on the ability of prescribers to follow recommendations made by the HYVET study.

4.3 Methods

4.3.1 Data collection

I undertook a retrospective cohort study of newly referred patients aged 80 years or over, who had attended the Hypertension Research Clinic at the Wellcome Trust Clinical Research Facility, University Hospital Birmingham NHS Trust, over a 10 year period (April 1998 to May 2008). As this study only analysed retrospective data contained within a pre-existing research database and clinic letters, ethical approval was not required for the study.

The clinic described runs as part of the Hypertension Service at the trust, and deals with around 500 new referrals per year. Most patients are referred by their GPs, and all first attend a specialist nurse-led screening clinic, where they have a series of baseline investigations as part of the routine clinical service. These include office blood pressure measurements, ambulatory blood pressure monitoring (ABPM), a series of blood tests including serum urea and electrolytes, cholesterol, and uric acid, a 12 lead electrocardiogram, urinanalysis, and body mass index (BMI) measurements. They then attend a clinician-led clinic, with the results from their screening clinic attendance. A full assessment of the patient is undertaken at this clinic, including a full history, examination, and review of their antihypertensive medications including any adverse effects. A review of their investigations is also undertaken, and diagnosis made primarily based on average ABPM readings.

Since May 2006, data relating to all newly referred patients attending the clinic, including the above measurements, has been entered into a hypertension database (Microsoft Access 2002) at the research facility. I identified patients either from this electronic database, or

from clinic letters in paper-based medical records dating from 1998, when the clinic was first set up.

4.3.2 Inclusion Criteria

Only patients newly referred for hypertension aged 80 years and above at the time of clinic attendance between April 1998 and May 2008 were included in the study. Patients with missing key data were excluded.

For the purpose of this study, the following key data were extracted: conventional office blood pressure readings, mean daytime and night time 24 hour ABPM readings, current antihypertensive medications, clinical diagnosis made in the clinic based on mean ABPM readings, potential or actual ADRs experienced, and changes in medications or recommendations on management made following the clinic appointment. The reason for referral to the hypertension clinic, where given in the referral letter from the primary care provider of the patient, was also extracted. An attempt was made to search for any missing data by reviewing the patients' medical notes. All extracted data was then entered into a Microsoft Excel spreadsheet.

4.3.3 Analysis

All patients were categorised according to their clinic diagnosis based on their mean daytime ABPM measurements, and according to the diagnostic thresholds and treatment targets used in HYVET (See Table 4.1).

Table 4-1: Diagnoses defined by mean day time ABPM readings

ABPM diagnosis	Mean ABPM reading
Poorly controlled blood pressure:	≥140/75 mmHg
Confirmed hypertension:	≥150 mmHg systolic
Well controlled blood pressure:	<140/75 mmHg
White coat hypertension:	≤140/75 mmHg but office readings or first few readings on ABPM >150 mmHg
Overmedicated:	<130 mmHg systolic

The mean day time blood pressure was the principle parameter used to categorise blood pressure. An adjustment upward of 10 mmHg systolic and 5 mmHg diastolic was made to the mean day time readings to allow for the differences in home and office readings in accordance with British Hypertension Society Guidelines, as previously described. Thus in un-medicated patients, a diagnosis of hypertension was confirmed if the mean day time ABPM systolic reading was ≥150 mmHg. This corresponded with the diagnostic threshold of 160 mmHg used in the HYVET study. Patients who were already on treatment at the time of the clinic referral were considered to have 'well controlled blood pressure' if their mean day time ABPM was <140/75 mm Hg or 'poorly controlled blood pressure' if it was ≥140/75

mmHg. This corresponded to the treatment target of 150/80 mmHg used in the HYVET study.

For the purposes of my analysis, and taking the HYVET thresholds and targets into account, un-medicated patients were considered to have 'white coat hypertension' if the mean ambulatory blood pressure was <140/75 mmHg, but the first few readings on ABPM (or clinic readings) were >150 mmHg. For the purpose of my study, patients on antihypertensive treatment where classed as having a 'white coat effect' if office/clinic blood pressure measurements showed a transient rise of greater than 10 mm Hg when compared to mean 24 hour ABPM readings. Patients on antihypertensive treatment were considered to be over-medicated if the mean ambulatory blood pressure was <130 mmHg systolic.

4.4 Results

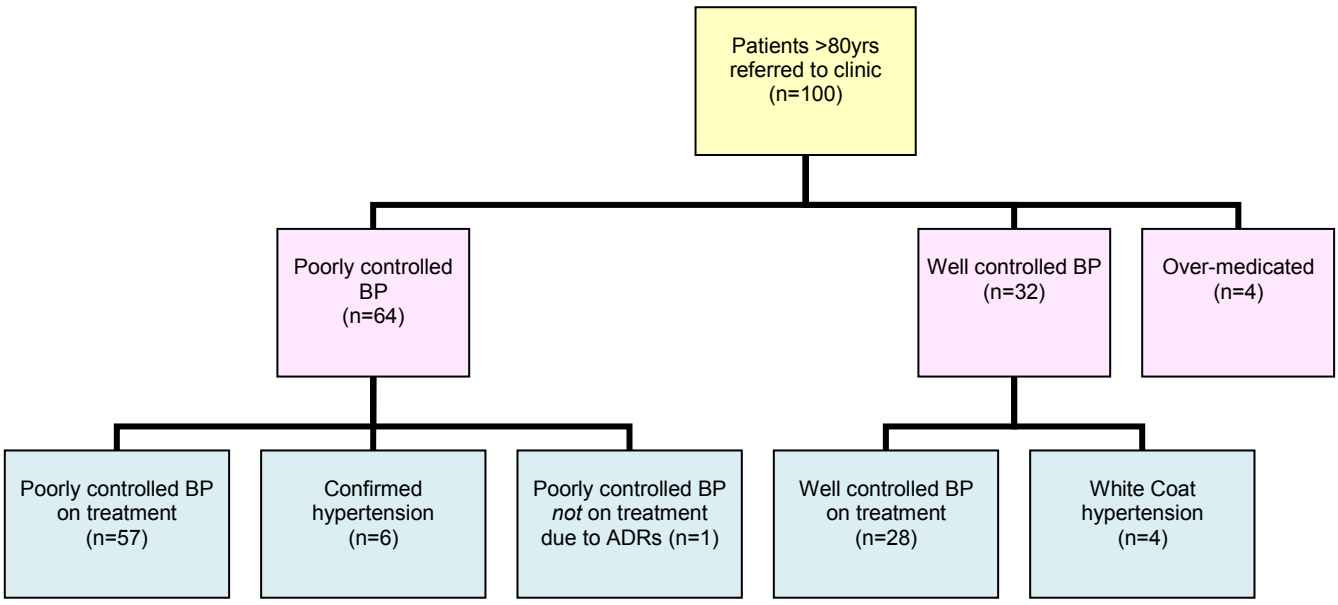
4.4.1 Demographics

A total of 106 patients were identified who were aged 80 years or over at time of referral, between April 1998 and May 2008. Six patients were excluded because of missing key data. Of the 100 patients who were included in the study, the age range was 80 to 94 years, with a mean age of 83 years. The commonest reason for referral to the hypertension clinic was 'difficult to control hypertension'.

4.4.2 Diagnostic categories

The diagnostic codes assigned to patients based on their mean day time ABPM readings at their first clinic attendance are outlined in Figure 4-1.

Figure 4-1: Diagnoses at clinic based on mean daytime ABPM reading



4.4.3 Poorly controlled BP group

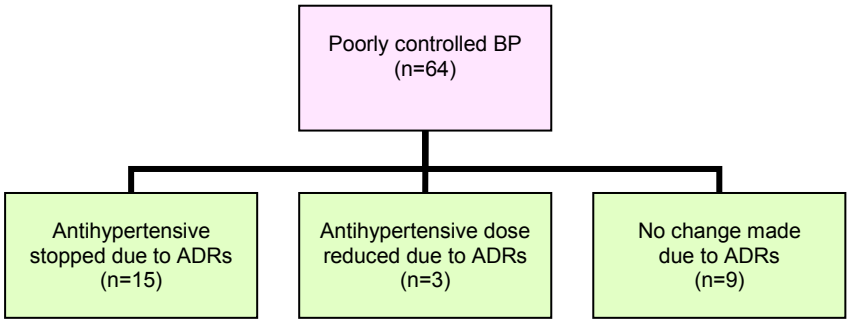
Following their initial assessment in the secondary care hypertension clinic, and prior to any changes to their current treatment, most patients (64/100) were diagnosed with 'poorly controlled blood pressure' on the basis of ABPM (mean day time pressure ≥140/75 mmHg). Fifty-seven of these patients were on treatment at the time ABPM was undertaken, and six patients were un-medicated, and thus had a diagnosis of confirmed hypertension made. One patient was un-medicated at the time of referral, despite the referring general practitioner having already made a diagnosis of hypertension; this was because the patient had experienced ADRs to multiple antihypertensive agents in the community.

Of the 64 poorly controlled patients**,** 38 patients were appropriately started on an additional antihypertensive according to the British Hypertension Society guidelines (Williams et al 2004), or had the dose of an existing antihypertensive increased, in order to achieve treatment targets. In 17 patients however, although an additional agent was added to reduce blood pressure, one (or more) of their existing antihypertensives were either stopped, or the dose reduced, predominantly as a result of ADRs. In addition, eight patients had no change made to their medications despite poor blood pressure control because previous ADRs precluded further intervention (See Figure 4-2), and one confirmed hypertensive remained un-medicated due to ADRs.

Although the majority of patients experienced actual ADRs which resulted in stopping/reducing medication or limiting treatment options, treatment options were limited in some due to the potential risk of developing ADRs e.g. the potential of developing

worsening oedema with amlodipine in a patient who already had marked peripheral oedema (See table 4-2).

Figure 4-2: Influence of ADRs on management of patients with poorly controlled BP



Actual ADRs previously experienced which limited treatment options in this group included ankle oedema secondary to amlodipine, hyponatraemia due to thiazide diuretics, and fatigue secondary to beta-adrenoceptor blockers (See table 4-3). One patient from this group also had a large variability in blood pressure on ABPM, increasing the risk of hypotensive episodes with addition of further therapy.

Finally, 12 patients in the poorly controlled group also had a marked 'white coat' effect (WCE) identified on the ABPM which would have led to aggressive escalation of therapy if GP surgery and/or clinic readings were used to guide management.

Table 4-2: Potential ADRs documented limiting treatment options in patients of 80 years or over with poorly controlled blood pressure on ABPM

Antihypertensive agent	Potential ADR limiting treatment options
Beta-adrenoceptor blockers (n=3) Sotalol 'Beta blockers in general'	'General intolerance'
Alpha blockers (n=1) Doxazocin	Peripheral oedema
Potassium sparing diuretics (n=1) Spironolactone	Hyponatraemia
Calcium channel antagonists (n=1) Amlodipine	Peripheral oedema

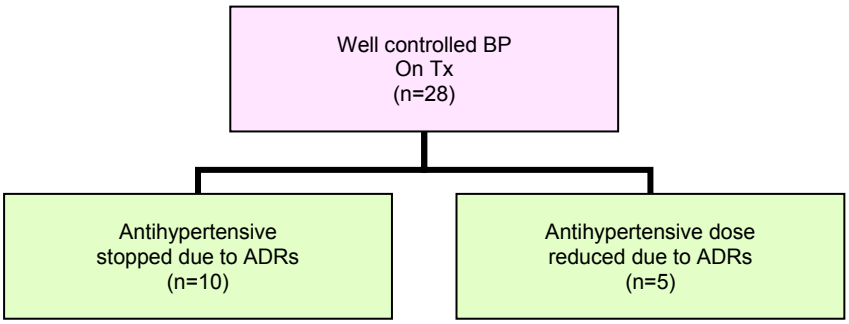
Table 4-3: Actual ADRs documented in patients of 80 years or over with poorly controlled blood pressure on ABPM

Antihypertensive agent	ADRs/reasons for stopping, reducing dose, or limiting treatment options
Beta-adrenoceptor blockers (n=4) Atenolol Bisoprolol	First degree heart block (1), fatigue (2), bradycardia (1)
Thiazide diuretics (n=7) Bendroflumethiazide	'Intolerant' (1), hyponatraemia (3), development of type 2 diabetes (1), gout (1), polyuria (1)
Calcium channel antagonists (n=8) Amlodipine Diltiazem Verapamil Felodipine Nifedipine	Ankle oedema (3), bradycardia (1), 'reacted badly' (1), headache (1), 'unwell' (2), gastrointestinal upset (1)
Alpha blockers (n=2) Doxazosin	Urinary frequency (1), 'Blackout' (1)
Centrally acting agents (n=1) Moxonidine	'Intolerant' (1)
ACE-inhibitors/ARBs (n=4) Enalapril Losartan Lisinopril Valsartan	'Intolerant' (2) 'Felt sick' (1) Cough (1)

4.4.4 Well controlled BP group

28/100 patients did not warrant any further intervention, as the blood pressure was well controlled on treatment. Thirteen of these patients appropriately had no change made to their treatment. Half of the patients from this group (14/28), however, had an antihypertensive agent stopped and/or the dose reduced due to ADRs, despite good blood pressure control (See Figure 4-3).

Figure 4-3: Influence of ADRs on management of patients with well controlled BP



Reported ADRs included ankle oedema (calcium channel blockers), headache (ACE inhibitor), cold extremities and bradycardia (beta-adrenoceptor blockers), hyponatraemia (Angiotensin receptor blockers or ARBs), and worsening renal function (ARB, ACE-inhibitor and thiazide diuretics) (See Table 4-4). Two patients also had marked blood pressure variability with hypotensive episodes on ABPM, and as a result had treatment withdrawn despite being well controlled on average. Only seven patients, who had an antihypertensive agent stopped, were started on an alternative agent in its place. This was not

possible in the remainder, as ADRs precluded addition of an alternative agent. A WCE was also identified in half (14/28) of this group.

Table 4-4: ADRs documented in elderly patients with well controlled blood pressure on ABPM

Antihypertensive agent	ADRs/reasons for stopping, reducing dose, or limiting treatment options
Beta adrenoceptor blockers (3) Atenolol	Cold extremities (1), 'intolerant' (1), fatigue and dyspnoea (1)
Thiazide diuretics (1) Bendroflumathiazide	Constipation (1)
Loop/potassium sparing diuretic (1) Co-amilofruse	Renal impairment (1)
Calcium channel antagonists (2) Diltiazem	Constipation (1), ankle oedema (1)
Alpha blockers (2) Doxazosin	Muscle cramps (1), rhinitis (1)
Centrally acting agents (1) Moxonidine	'Symptomatic' (1)
ACE-inhibitors/ARBs (5) Telmisartan Losartan Ramipril Candesartan Lisinopril	Hyponatraemia (1), 'intolerant' (1), headache (1), renal impairment (2)

4.4.5 Over-medicated group

Four patients were found to be over-medicated and had very low blood pressures on ambulatory monitoring. Two of these patients had been referred with 'difficult to control BP'; data was not available for the remaining two. One patient from this group was found to have a WCE. All four patients appropriately had one or more antihypertensive agents stopped to avoid postural symptoms.

4.4.6 White Coat Hypertension group

Four un-medicated patients were diagnosed with white coat hypertension and therefore did not need treatment (See Figure 4-1).

As previously described, 27 additional patients from the poorly controlled, well controlled and overmedicated groups had evidence of a WCE.

Finally, no patients were found to have 'masked' or 'reverse white coat' hypertension.

4.5 Discussion

4.5.1 ADRs limiting treatment

The current study highlights the difficulties of managing hypertension in very elderly patients even with relatively modest blood pressure targets (150/80 mmHg), due to the high incidence or increased risk of actual or potential ADRs respectively. The ADRs documented in my cohort were consistent with those identified in previous epidemiological studies focusing on ADRs in the elderly. Almost half the patients had documented ADRs which limited further intervention (40/100) or had very low blood pressure which necessitated withdrawal of therapy (4/100) to avoid troublesome postural symptoms. These results suggest that aggressive treatment of hypertension in the very elderly may be difficult to achieve in practice, due to the high incidence of ADRs and poor tolerability of drugs in this age group.

As discussed previously, there are several reasons why older people may be more vulnerable to ADRs, including age-related changes in pharmacokinetics and pharmacodynamics, and impaired cardiac, renal, and baroreceptor function. Several studies have confirmed the high incidence of ADRs in elderly patients taking antihypertensives, and these agents are a frequent cause of ADRs leading to hospital admission. Polypharmacy may also be a contributing factor, and is both common in the treatment of hypertension, and in elderly patients in general.

It is unsurprising that a proportion of patients in my study also had periods of very low blood pressure necessitating the withdrawal of therapy. The prevalence of postural or orthostatic

hypotension has been reported to be between 10% and 30% for elderly people and is particularly associated with the use of antihypertensive medication (Mets 1995). As discussed previously, this may be due to a number of factors, including reduced clearance of antihypertensive drugs, and impaired baroceptor function in the elderly (Salzman 2005).

4.5.2 Comparison with findings from HYVET

The HYVET study provided compelling evidence that treating hypertension to a target blood pressure of 150/80 mm Hg in the very elderly is beneficial. Active treatment was associated with impressive reductions in stroke rates, deaths from any cause and heart failure. Interestingly though, there was a very low incidence of medication-related adverse events during the trial. This is inconsistent with results from the current study, but there may be a number of reasons for this. Firstly, it is likely that patients selected for HYVET were in general, healthier than the average elderly population. Exclusion criteria for the HYVET study included previous haemorrhagic stroke, heart failure requiring treatment with antihypertensive medication, renal impairment, and a diagnosis of dementia. These conditions are common in the elderly and are associated with an increased risk of ADRs. For example, we know that some ADRs are related to toxicity as a result of renal impairment, and cognitive impairment can affect concordance with drug therapy, which in turn can increase the risk of adverse effects. It is also likely that patients included in the HYVET study were on fewer medications as had fewer comorbidities, and hence had a lower risk of developing ADRs, although data for this is lacking from the published trial. Of course, it is important to note that as the data available for my analysis was limited to that contained

within the research database, I was unable to determine whether any of my cohort had comorbidities which would pre-dispose them to ADRs.

Secondly, in my study, elderly patients had been referred to a specialist hypertension clinic in secondary care for further management, as their general practitioners were having difficulty in controlling their blood pressure and achieving targets. A number of these patients had already experienced ADRs in the community which precluded further intervention at presentation to the specialist clinic. It is likely therefore, that patients included in my study were at the extreme end of the spectrum of the elderly hypertensive population in the community.

Finally, and most importantly, the majority of ADRs experienced by my cohort could be classed as minor, whereas HYVET only reported serious adverse events.

4.5.3 The White Coat Effect

The commonest documented reason for referral to the clinic was 'difficult to control blood pressure'; it is unsurprising therefore, that the majority of patients who had been referred to the clinic were found to have poorly controlled blood pressure on ABPM. However, a significant proportion of elderly patients were found to have a marked 'White coat effect' on ABPM (31/100); twelve patients in the poorly controlled group, fourteen in the well controlled group, one in over-medicated group, and four un-medicated patients who were diagnosed with white coat hypertension.

It is clear therefore, that had diagnoses been made based on clinic readings in the community rather than based average 24 hour ABPM readings, this may have led to inappropriate escalation in antihypertensive medication, and hence an increased risks of ADRs, drug interactions, and hypotensive episodes in an already 'at risk' group. My study therefore also demonstrates the usefulness of using 24 hour ABPM, even in the very elderly.

4.5.4 Limitations

This was a retrospective study and was limited to the collection and analysis of data contained within a pre-existing database or clinic letters. I was therefore unable to analyse other data, for example, data related to comorbidities or other medications, both of which might increase the susceptibility to ADRs. In addition, due to the retrospective nature of my study, I was unable follow up patients to determine the impact of treatment limitations due to ADRs, on long-term blood pressure control, morbidity, and mortality. Finally, the majority of elderly patients included in my study were attending a secondary care clinic because of poorly controlled blood pressure, so may not be representative of very elderly patients managed in primary care.

Some of the limitations described above might be addressed by undertaking a prospective community-based study, which would also allow a larger sample to be recruited; such a study would of course, require ethical approval, and how this might be undertaken is discussed in Chapter 5.

4.5.5 Conclusions

In conclusion, my study highlights the challenge of prescribing antihypertensive medication in very elderly patients and suggests that a high incidence of ADRs may preclude treatment of hypertension to a target of 150 mmHg. My findings also suggest that ambulatory monitoring may have an important role in managing these patients. In particular, ambulatory monitoring may be useful in identifying those who have evidence of a 'white coat effect' in a bid to avoid inappropriate escalation of therapy, and a further increased risk of ADRs. Although the study is limited by the fact that the patients included may not be representative of very elderly patients managed in primary care, my findings still suggest that careful monitoring of very elderly patients taking antihypertensive agents is needed.

5 CHAPTER 5- CONCLUSIONS AND FUTURE RESEARCH

5.1 Patient experience of ADRs

Through interviewing survivors, and analysing internet narratives of those who had personal experience of drug-induced SJS and TEN, I found that ADRs have a significant burden in terms of their impact on patients' lives. I was able to construct a framework of their experiences, which included the circumstances leading to the ADR, and difficulties encountered in both getting a diagnosis of the ADR and in its subsequent management. I also explored patients' interpretations of why the ADR occurred, and found that many believed that the ADR could have been avoided. This, along with negative experiences at the time of the event, such as lacking information or poor communication by healthcare professionals, influenced their trust in healthcare professionals and medicines in general. The ADR continued to affect patients' lives long after the event, both physically and psychologically. Many were left fearful of medicines in general and some described unsubstantiated fears. Patients and relatives found the internet a useful source of information about the ADR at the time of the event, and many posted on support group websites to share their experiences of the ADR and to seek advice from others regarding the many concerns they had. The concerns expressed by patients and their relatives implied that they had many unanswered questions regarding the ADR, both at the time of the event, and long afterwards, and my findings might therefore be helpful in guiding healthcare professionals in communicating and managing those experiencing the ADR more effectively in the future.

I also identified a large number of internet descriptions of the ADR, despite its rarity, emphasising the potential value of analysis of internet descriptions of patient experience in

rare disorders, where engagement with patients to understand their experiences and views might otherwise be difficult.

But how might my findings be used to improve the management of patients with ADRs in practice? How might they be built upon, and what do they imply for future research?

As my qualitative work generated a number of hypotheses, further research would be useful in testing some these hypotheses where possible. It is likely that a quantitative approach would be required to achieve this, and a retrospective questionnaire-based study of survivors would be one option. Such a questionnaire might include closed questions, with 'scaled' responses required for some (e.g. using a Likert scale), and open questions, with the opportunity for the respondent to provide free text answers. Questions included might focus, for example, on aspects of the care patients received both in the community and in hospital, on their interpretations of why the ADR occurred, the impact of the ADR on their current lives, and their attitudes towards medicines. The main difficulty with this approach would be the small number of survivors available due to the rarity and high mortality associated with the ADR. A national multi-centre study, however, might allow a larger number of survivors to be recruited to such a study. It might also allow purposive sampling to ensure adequate representation of the available population of survivors, in terms of age, gender etc. Groups within the sample could therefore be compared. Those who were managed in specialist burns units for example, could be compared with those who were not, in order to test my hypothesis that those managed in a burns unit may have more positive experiences.

Other suggestions from my research, such as reducing the avoidance of necessary medicines after the event by providing patient education and support, could be tested with a randomised controlled trial, comparing reported avoidance behaviour in those who received education after the ADR, and in those who did not. Similarly, interventions such as providing

psychological support or counselling after discharge from hospital for those experiencing long-term sequelae could also be piloted.

In addition, subjective data from patients experiencing ADRs might be supplemented by data obtained from their hospital medical and nursing records. This may, for example, be helpful in exploring differences between patients' recollections or perceptions of events associated with their ADR-related admission, and events as documented by healthcare professionals. As discussed in 2.5.2, one problem with undertaking a retrospective analysis is the potential for recollection bias, particularly in those who experienced the ADR many years previously. A prospective study might minimise such a bias; however, it is likely that many patients would be too unwell to participate during the acute event, and any analysis would have to be undertaken soon after they had recovered from the episode.

In this thesis, I chose to examine experiences of serious ADRs, and focused primarily on drug-induced SJS and TEN. It would be interesting however, to determine whether or not patients experiencing other serious ADRs, such life-threatening upper gastrointestinal haemorrhage due to NSAIDs, for example, have similar experiences, views, and perceptions to those expressed by SJS and TEN sufferers. SJS and TEN are known to cause long-term sequelae, and it would be interesting, for example, to determine whether or not other serious ADRs that don't commonly do so, have the same impact on patients. It is likely that patients experiencing minor ADRs (which do not require hospital admission) would have different experiences to those with serious ADRs requiring admission to an intensive care unit. It would be interesting, however, to explore whether or not those experiencing minor ADRs have different views for example, on the safety of medicines, compared to those who experienced more serious ADRs.

This thesis also explored the perceptions that patients had of the healthcare professionals who: i) initially assessed them when they presented with the ADR; ii) managed them when they were admitted to hospital; and iii) currently assessed them for other problems. One interesting perception of patients was that healthcare professionals who initially misdiagnosed their ADR for another condition, 'felt guilty' as a result. In addition, some perceived that the healthcare professionals who had prescribed the culprit drug appeared anxious and 'defensive' after the ADR occurred. Following on from this, an exploration of the views and perceptions of such healthcare professionals might be considered as a potential area for further research. Healthcare professionals aim to prescribe medicines to help their patients 'feel better', and at the same time, 'do no harm'. Hence, when an ADR does occur, it is possible that healthcare professionals may feel responsible for its occurrence, even if it could not be reasonably predicted or prevented. It is also possible that such an occurrence may influence their future prescribing of the implicated drug, or their prescribing behaviour in general. A qualitative study exploring how healthcare professionals react after their patient develops a serious ADR as a result of a medicine they prescribed, would shed light on this area, and would therefore be of great interest.

My analysis of internet descriptions of self-identified ADRs found that patients and their relatives had many unanswered questions and concerns regarding the ADR they experienced. Many also felt that they lacked information, both during and after the event. With this in mind, there may be a number of ways in which this perceived lack of information and the common concerns expressed, might be anticipated and addressed in future patients. One approach might involve creating and piloting a patient information leaflet focused around these common concerns, and on providing answers to commonly asked questions. It may also be helpful to pilot a checklist for healthcare professionals, informed by the findings

from this thesis, consisting of topics to be discussed with patients prior to, or soon after discharge from hospital. Resources providing this information digitally could also be considered, including information CDs (compact discs) or DVDs (digital video discs). Finally, we know that many of those posting their experiences on internet websites, did so as they wanted to share their experiences, and others gained considerable support from this. Using existing patient experience to help others experiencing ADRs may therefore be of great potential. Patients and relatives who are not aware of existing support group websites for SJS and TEN, might therefore be directed to them by healthcare professionals. However, as discussed in Chapter 3, the accuracy of information and the authenticity of many of the experiences described on such websites can often not be verified. In addition, information on such websites may not be presented in a structured or systematic way to allow the user to easily access the information they require; for example, users may need to read through numerous internet postings to find the answer to a particular question. We do, however, know of other websites, which are regulated and have input from healthcare professionals, to ensure that the information presented is as balanced and accurate as is possible. As previously discussed, one such website is run by a charity called DIPEx (Herxheimer et al. 2000). This website uses a multimedia approach (e.g. visually recorded and structured interviews of patients discussing their experiences of a wide variety of conditions), and links these patient experiences with evidence-based information about treatments and the illness itself, along with a range of other resources that may be useful to patients, including links to support group websites. At the time of writing this thesis, serious ADRs were not featured on DIPEx or other similar websites; liaising with the organisers of such websites to include serious ADRs might therefore be a way forward.

I also found that many individuals posting their experiences of the ADR were motivated to do so, as they wished to raise awareness regarding the ADR and the culprit drug responsible. The suspected drug was indicated in 89% of cases believed to be drug-related. This highlights the potential usefulness of patient internet descriptions or reports of ADRs, in providing additional information for healthcare professionals and the pharmaceutical industry. More research however, is required to determine the quality of such reports, and whether or not they could be used to detect new ADRs. In particular, it would be important to determine what proportion of internet reports or descriptions from non-company sponsored patient websites contain adequate information to allow the accurate diagnosis and classification of an ADR. This was not explored in the current thesis, but could however be investigated by applying the elements of an ADR description prototype such as that described by Dewitt and Sorofman (1999), as discussed in 1.2.7. In addition, it is important to note that none of the patient websites identified through my research, were set-up to identify and report ADRs (unlike government pharmacovigilance websites hosted by the FDA or MHRA, for example), as their primary purpose was to share experiences and to connect people with similar conditions. This of course, may have an impact on the type of information provided in descriptions posted on them.

Finally, a number of internet descriptions included authors' names and contact details, such as email addresses. Data within internet descriptions could therefore potentially be confirmed and further data collected by contacting description authors in a further study. Such a study, however, would require ethical approval.

5.2 The impact of ADRs on managing hypertension in the very elderly

This thesis also explored the impact of ADRs on the appropriate management of hypertension in the very elderly, as recommended by HYVET (Beckett et al. 2008). I found that the aggressive treatment of hypertension in the very elderly as recommended by the authors of HYVET, was difficult to achieve in secondary care due to a high incidence of ADRs and symptoms of postural hypotension.

Although the ADRs experienced could not be classed as serious, in that they did not require hospital admission or result in significant disability (Edwards & Aronson 2000), they were significant enough to either necessitate withdrawal of therapy, or to require a reduction in the dose of the culprit antihypertensive agent at their first presentation to our specialist hypertension clinic. As a result of both ADRs previously experienced, and ADRs present at the time of their first attendance at our clinic, many of the elderly patients referred to our clinic could not be managed optimally according to HYVET recommendations.

But what are the implications of my findings in terms of managing such patients, and how might future research in this area be planned? Firstly, as discussed in Chapter 4, there are a number of limitations of this study, which may be addressed through further research. My aim was in fact to principally focus on the impact of ADRs in secondary care. Nonetheless, by the very virtue of having been referred to a specialist clinic in secondary care, my cohort was likely to be at the extreme end of the spectrum of the elderly hypertensive population in the community, and hence, not representative of very elderly patients managed in primary care. As discussed in Chapter 4, we know that the prevalence of hypertension in the general elderly population is high (Williams et al. 2004), but only a relatively small number of patients (106 in total) aged 80 years or over were referred to the clinic over a ten year period.

In addition, the majority of these patients were referred as their general practitioners were already having difficulty in controlling their blood pressure, with a number having already experienced ADRs in the community.

In view of this, a study of the impact of ADRs experienced by the very elderly in the community might be useful. Such a study would allow a larger sample to be studied, and one which would be representative of the elderly population in general. In addition, a community-based study would allow a prospective analysis, due to the larger number of available patients. Many of the limitations of undertaking a retrospective study such as the one presented in this thesis might therefore be overcome, including having limited data available for analysis (i.e. only data contained within patients' letters or database records), and difficulties in attempting to find missing data retrospectively.

As a significant number of elderly patients in my study were unable to have their hypertension managed optimally according to HYVET guidelines, primarily due to ADRs, it could therefore be questioned whether or not such patients should be referred to secondary care in the first place. Based on my findings, I feel that the answer to this question should be in the affirmative, for the reasons I will now outline. Firstly, many of the elderly patients in my cohort were still taking antihypertensives which were causing intolerable ADRs, and these were stopped when they presented to our clinic. It was not possible from the data available, to determine whether or not their GPs had recognised these ADRs, but it is clear that appropriate action (i.e. reducing the dose or withdrawing the culprit drug) had not been undertaken. If their GPs were indeed aware, there may have been a number of reasons for the described inaction, including wanting to get a specialist opinion before instituting a change in therapy, or the fear of worsening blood pressure control; further research into this area may therefore be useful.

In addition, a significant proportion of patients were in fact found to have a previously undiagnosed 'white coat effect' on 24 hour ABPM at our clinic. Hence, had diagnoses been made based on clinic readings in the community, rather than based on average 24 hour ABPM readings, this may have led to inappropriate escalation in antihypertensive medication, and hence an increased risks of ADRs, drug interactions, and hypotensive episodes in an already 'at risk' group.

My study therefore highlights the usefulness of 24 hour ABPM, which may reduce the risk of overmedicating patients and thus reduce the risk of ADRs. Further research to determine the actual risk reduction in ADRs associated with such an intervention, would, however be needed.

5.3 Conclusions

This thesis has demonstrated that serious ADRs have a significant burden in terms of their impact on patients' lives; their experiences at the time of the event, and their beliefs regarding why the ADR occurred, may influence their future trust in healthcare professionals and in medicines in general.

In addition, through an analysis of internet narratives of those experiencing SJS and TEN, this thesis has shown that sufferers have many unanswered questions and concerns regarding the ADR, and thus proposes that healthcare professionals might improve the management and experience of such patients by providing information focusing on common concerns, and improving communication at the time of the event.

Finally, I have shown that ADRs have a significant impact on managing hypertension optimally in very elderly patients referred to secondary care, and that a high incidence of ADRs may preclude treatment of hypertension to a target blood pressure of 150 mmHg as recommended by current guidelines. A cautious approach when managing such patients may therefore be required.

References

Albrecht, S., Ihmsen, H., Hering, W., Geisslinger, G., Dingemanse, J., Schwilden, H., & Schuttler, J. 1999. The effect of age on the pharmacokinetics and pharmacodynamics of midazolam. *Clinical Pharmacology & Therapeutics*, 65, (6) 630-639 available from: WOS:000081145500005

Amery, A., Birkenhager, W., Brixko, P., Bulpitt, C., Clement, D., Deruyttere, M., Deschaepdryver, A., Dollery, C., Fagard, R., Forette, F., Forte, J., Hamdy, R., Henry, J.F., Joossens, J.V., Leonetti, G., Lundjohansen, P., Omalley, K., Petrie, J., Strasser, T., Tuomilehto, J., & Williams, B. 1985. Mortality and Morbidity Results from the European Working Party on High Blood-Pressure in the Elderly Trial. *Lancet*, 1, (8442) 1349-1354 available from: WOS:A1985AKB6200001

Anderson, M. & Choonara, I. 2010. A systematic review of safety monitoring and drug toxicity in published randomised controlled trials of antiepileptic drugs in children over a 10-year period. *Archives of Disease in Childhood*, 95, (9) 731-738 available from: WOS:000281003700015

Aronson, J.K. & Ferner, R.E. 2003. Joining the DoTS: new approach to classifying adverse drug reactions. *British Medical Journal*, 327, (7425) 1222-1225 available from: WOS:000186784300026

Aronson, J. 2002, "Drug Therapy ," *In Davidson's principles and practice of Medicine*, 19th ed. C. Haslett et al., eds., Edinburgh: Elsevier Science, pp. 147-163.

Arvidson, J., Kildal, M., Linde, T., & Gedeborg, R. 2007. Toxic epidermal necrolysis and hemolytic uremic syndrome after allogeneic stem-cell transplantation. *Pediatric Transplantation*, 11, (6) 689-693

Atkin, P.A., Veitch, P.C., Veitch, E.M., & Ogle, S.J. 1999. The epidemiology of serious adverse drug reactions among the elderly. *Drugs & Aging*, 14, (2) 141-152 available from: WOS:000078806000005

Auquier-Dunant, A., Mockenhaupt, M., Naldi, L., Correia, O., Schroder, W., & Roujeau, J.C. 2002. Correlations between clinical patterns and causes of erythema multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis - Results of an international prospective study. *Archives of Dermatology*, 138, (8) 1019-1024 available from: WOS:000177499100003

Avery, A.J., Anderson, C., Bond, C.M., Fortnum, H., Gifford, A., Hannaford, P.C., Hazell, L., Krska, J., Lee, A.J., McLernon, D.J., Murphy, E., Shakir, S., & Watson, M.C. 2011. Evaluation of patient reporting of adverse drug reactions to the UK 'Yellow Card Scheme': literature review, descriptive and qualitative analyses, and questionnaire surveys. *Health Technology Assessment*, 15, (20) 1-+ available from: WOS:000292483700001

Aymanns, C., Keller, F., Maus, S., Hartmann, B., & Czock, D. 2010. Review on Pharmacokinetics and Pharmacodynamics and the Aging Kidney. *Clinical Journal of the American Society of Nephrology*, 5, (2) 314-327 available from: WOS:000274703400023

Bachot, N., Revuz, J., & Roujeau, J.C. 2003. Intravenous immunoglobulin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis - A prospective noncomparative study showing no benefit on mortality or progression. *Archives of Dermatology*, 139, (1) 33-36 available from: WOS:000180456700005

Bachot, N. & Roujeau, J.C. 2003. Differential diagnosis of severe cutaneous drug eruptions. *American Journal of Clinical Dermatology*, 4, (8) 561-572 available from: WOS:000185801800006

Baglin, A., Boulard, J.C., Hanslik, T., & Prinseau, J. 1995. Metabolic Adverse Reactions to Diuretics - Clinical Relevance to Elderly Patients. *Drug Safety*, 12, (3) 161-167 available from: WOS:A1995QL67400002

Baikie, K. A. & Wilhelm, K. Emotional and physical health benefits of expressive writing. Advances in Psychiatric Treatment 11, 338-346. 2005.
Ref Type: Journal (Full)

Barry, C.A., Bradley, C.P., Britten, N., Stevenson, F.A., & Barber, N. 2000. Patients' unvoiced agendas in general practice consultations: qualitative study. *British Medical Journal*, 320, (7244) 1246-1250 available from: WOS:000086981400021

Basile, J. 2009. New Therapeutic Options in Patients Prone to Hypertension: A Focus on Direct Renin Inhibition and Aldosterone Blockade. *American Journal of the Medical Sciences*, 337, (6) 438-444 available from: WOS:000267131900010

Bastuji-Garin, S., Fouchard, N., Bertocchi, M., Roujeau, J.C., Revuz, J., & Wolkenstein, P. 2000. SCORTEN: A severity-of-illness score for toxic epidermal necrolysis. *Journal of Investigative Dermatology*, 115, (2) 149-153 available from: WOS:000088805800002

Bastuji-Garin, S., Rzany, B., Stern, R.S., Shear, N.H., Naldi, L., & Roujeau, J.C. 1993. Clinical Classification of Cases of Toxic Epidermal Necrolysis, Stevens-Johnson Syndrome, and Erythema Multiforme. *Archives of Dermatology*, 129, (1) 92-96 available from: WOS:A1993KH22800020

Beckett, N.S., Peters, R., Fletcher, A.E., Staessen, J.A., Liu, L.S., Dumitrascu, D., Stoyanovsky, V., Antikainen, R.L., Nikitin, Y., Anderson, C., Belhani, A., Forette, F., Rajkumar, C., Thijs, L., Banya, W., & Bulpitt, C.J. 2008. Treatment of hypertension in patients 80 years of age or older. *New England Journal of Medicine*, 358, (18) 1887-1898 available from: WOS:000255387900003

Beckey, C., Lundy, A., & Lutfi, N. 2007. Lercanidipine in the treatment of hypertension. *Annals of Pharmacotherapy*, 41, (3) 465-474 available from: WOS:000245183000012

Beers, M.H., Ouslander, J.G., Rollingher, I., Reuben, D.B., Brooks, J., & Beck, J.C. 1991. Explicit Criteria for Determining Inappropriate Medication Use in Nursing-Home Residents. *Archives of Internal Medicine*, 151, (9) 1825-1832 available from: WOS:A1991GE53400019

Bigby, M. 2000. Incidence, prevalence and the rates of cutaneous reactions to drugs. *Journal of the European Academy of Dermatology and Venereology*, 14, (6) 435

Bigby, M., Jick, S., Jick, H., & Arndt, K. 1986. Drug-Induced Cutaneous Reactions - A Report from the Boston Collaborative Drug Surveillance Program on 15438 Consecutive Inpatients, 1975 to 1982. *Jama-Journal of the American Medical Association*, 256, (24) 3358-3363 available from: WOS:A1986F289300021

Bjertnaes, O.A., Sjetne, I.S., & Iversen, H.H. 2012. Overall patient satisfaction with hospitals: effects of patient-reported experiences and fulfilment of expectations. *Bmj Quality & Safety*, 21, (1) 39-46 available from: WOS:000298133900006

Blenkinsopp, A., Wilkie, P., Wang, M., & Routledge, P.A. 2007. Patient reporting of suspected adverse drug reactions: a review of published literature and international experience. *British Journal of Clinical Pharmacology*, 63, (2) 148-156 available from: WOS:000243376600003

Boshuizen, H.C., Izaks, G.J., van Buuren, S., & Ligthart, G.J. 1998. Blood pressure and mortality in elderly people aged 85 and older: community based study. *British Medical Journal*, 316, (7147) 1780-+ available from: WOS:000074286300024

Bowman, L., Carlstedt, B., Hancock, E., & Black, C. 1996. Adverse drug reaction (ADR) occurrence and evaluation in elderly inpatients. *Pharmacoepidemiology and Drug Safety*, 5, (1) 9-18

Braun, V. & Clarke, V. Using thematic analysis in psychology. Qualitative Research in Psychology 3[2], 77-101. 2006.
Ref Type: Journal (Full)

Breathnach 2010, "Erythema multiforme, Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis," *In Rook's Textbook of Dermatology*, Eighth ed. vol. 4 Burns T et al., eds., West Sussex: Wiley-Blackwell, p. 76.1-76.22.

Broncel, M., Chojnowska-Jezierska, J., & Adamska-Dyniewska, H. 1998. Bisoprolol in the treatment of hypertension in the elderly. *Journal of Human Hypertension*, 12, (9) 643-644 available from: WOS:000076252200017

Budnitz, D.S., Shehab, N., Kegler, S.R., & Richards, C.L. 2007. Medication use leading to emergency department visits for adverse drug events in older adults. *Annals of Internal Medicine*, 147, (11) 755-U26 available from: WOS:000251539100002

Cain, J. 2008. Online social networking issues within academia and pharmacy education. *American Journal of Pharmaceutical Education*, 72, (1) available from: WOS:000253427000010

Campbell, R. 2005. Consumer informatics: elderly persons and the Internet. *Perspectives in health information management*, 2, 2 available from:

Chan, H.L., Stern, R.S., Arndt, K.A., Langlois, J., Jick, S.S., Jick, H., & Walker, A.M. 1990. The Incidence of Erythema Multiforme, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis - A Population-Based Study with Particular Reference to Reactions Caused by Drugs Among Outpatients. *Archives of Dermatology*, 126, (1) 43-47 available from: WOS:A1990CH25800004

Chang, C.M., Liu, P.Y.Y., Yang, Y.H.K., Yang, Y.C., Wu, C.F., & Lu, F.H. 2005. Use of the beers criteria to predict adverse drug reactions among first-visit elderly outpatients. *Pharmacotherapy*, 25, (6) 831-838 available from: WOS:000229496000008

Charmaz, K. 2006. *Constructing Grounded Theory. A Practical Guide Through Qualitative Analysis*, First ed. London, SAGE Publications.

Chavanu, K., Merkel, J., & Quan, A.M. 2008. Role of ambulatory blood pressure monitoring in the management of hypertension. *American Journal of Health-System Pharmacy*, 65, (3) 209-218 available from: WOS:000253102600010

Chave, T.A., Mortimer, N.J., Sladden, M.J., Hall, A.P., & Hutchinson, P.E. 2005. Toxic epidermal necrolysis: current evidence, practical management and future directions. *British Journal of Dermatology*, 153, (2) 241-253 available from: WOS:000230842300001

Cherubini, A., Fabris, F., Ferrari, E., Cucinotta, D., Incalzi, R.A., & Senin, U. 2003. Comparative effects of lercanidipine, lacidipine, and nifedipine gastrointestinal therapeutic system on blood pressure and heart rate in elderly hypertensive patients: the ELderly and LErcanidipine (ELLE) study. *Archives of Gerontology and Geriatrics*, 37, (3) 203-212 available from: WOS:000185774900002

Chung, W., Hung, S., Hong, H., Hsih, M., Yang, L., Ho, H., Wu, J., & Chen, Y. 2004. Medical genetics: A marker for Stevens-Johnson syndrome. *Nature*, 428, 486

Chung, W., Hung, S., & Chen, Y. 2007. Human leukocyte antigens and drug hypersensitivity. *Current opinion in Allergy and Clinical Immunology*, 7, (4) 317-323

Ciaccio, C.E. & Saltoun, C.A. 2008. Fatal toxic epidermal necrolysis after rechallenge with lansoprazole. *Annals of Allergy Asthma & Immunology*, 100, (1) A71 available from: WOS:000252212800243

Committee on Quality of Health Care in America, I. o. M. 2001, *Crossing the Quality Chasm: A New Health System for the 21st Century.*, National Academy Press.

Corbin, J. & Strauss, A. 2008. *Basics of qualitative research: Techniques and Procedures for Developing Grounded Theory.*, Third ed. London, Sage Publications.

Corcoran, T.B., Haigh, F., Seabrook, A., & Schug, S.A. 2009. The Quality of Internet-sourced Information for Patients With Chronic Pain Is Poor. *Clinical Journal of Pain*, 25, (7) 617-623 available from: WOS:000269331400010

Corsonello, A., Pedone, C., Corica, F., Mussi, C., Carbonin, P., & Incalzi, R.A. 2005. Concealed renal insufficiency and adverse drug reactions in elderly hospitalized patients. *Archives of Internal Medicine*, 165, (7) 790-795 available from: WOS:000228308800012

Crocco, A.G., Villasis-Keever, M., & Jadad, A.R. 2002. Analysis of cases of harm associated with use of health information on the Internet. *Jama-Journal of the American Medical Association*, 287, (21) 2869-2871 available from: ISI:000176002200034

Curb, J.D., Borhani, N.O., Blaszkowski, T.P., Zimbaldi, N., Fotiu, S., & Williams, W. 1985. Long-Term Surveillance for Adverse-Effects of Antihypertensive Drugs. *Jama-Journal of the American Medical Association*, 253, (22) 3263-3268 available from: WOS:A1985AJU3000020

Cuthbertson, B.H., Hull, A., Strachan, M., & Scott, J. 2004. Post-traumatic stress disorder after critical illness requiring general intensive care. *Intensive Care Medicine*, 30, (3) 450-455 available from: WOS:000189364300015

Dahlof, B., Lindholm, L.H., Hansson, L., Schersten, B., Ekbom, T., & Wester, P.O. 1991. Morbidity and Mortality in the Swedish Trial in Old Patients with Hypertension (Stop-Hypertension). *Lancet*, 338, (8778) 1281-1285 available from: WOS:A1991GR02300001

Daubeney, P.E.F. & Scopes, J.W. 1991. Recurrent Stevens-Johnson Syndrome. *Journal of the Royal Society of Medicine*, 84, (3) 168 available from: WOS:A1991FA23900017

Davies, E.C., Green, C.F., Taylor, S., Williamson, P.R., Mottram, D.R., & Pirmohamed, M. 2009. Adverse Drug Reactions in Hospital In-Patients: A Prospective Analysis of 3695 Patient-Episodes. *Plos One*, 4, (2) available from: WOS:000265484100009

Davis, M.D.P., Rogers, R.S., & Pittelkow, M.R. 2002. Recurrent erythema multiforme/Stevens-Johnson syndrome - Response to mycophenolate mofetil. *Archives of Dermatology*, 138, (12) 1547-1550 available from: WOS:000179804700001

Davison, K.P., Pennebaker, J.W., & Dickerson, S.S. 2000. Who talks? The social psychology of illness support groups. *American Psychologist*, 55, (2) 205-217 available from: ISI:000085629100001

Department of Health 2010, *Equity and excellence: Liberating the NHS*, Department of Health, United Kingdom.

Dewitt, J.E. & Sorofman, B.A. 1999. A model for understanding patient attribution of adverse drug reaction symptoms. *Drug Information Journal*, 33, (3) 907-920 available from: WOS:000082151100032

Dickerson, S.S., Boehmke, M., Ogle C, & Brown JK 2006. Seeking and managing hope: Patients' experiences using the internet for cancer care. *Oncology Nursing Forum*, 33, (1) 8-17

Dominick, J.R. 1999. Who do you think you are? Personal home pages and self-presentation on the World Wide Web. *Journalism & Mass Communication Quarterly*, 76, (4) 646-658 available from: ISI:000086118500003

Doring, N. 2002. Personal Home pages on the web: A review of Research. *Journal of Computer-mediated communication*, 7, (3)Accessed 31 August 2010.

Dormann, H., Krebs, S., Muth-Selbach, U., Criegee-Rieck, M., Radespiel-Troger, M., Levy, M., Hahn, E.G., Brune, K., & Schneider, H.T. 2001. Adverse drug reactions in patients with gastroenterological diseases: does age increase the risk? *Alimentary Pharmacology & Therapeutics*, 15, (2) 171-180 available from: WOS:000166548500005

Drayer, J.I.M., Weber, M.A., Deyoung, J.L., & Wyle, F.A. 1982. Circadian Blood-Pressure Patterns in Ambulatory Hypertensive Patients - Effects of Age. *American Journal of Medicine*, 73, (4) 493-499 available from: WOS:A1982PM29400007

Dunant, A., Sekula, P., Roujeau, J.C., Naldi, L., Halevy, S., & Davidovici, B. 2008. Quality of life one year after Stevens-Johnson syndrome (SJS) and toxic epidermal Necrolysis (TEN). *Pharmacoepidemiology and Drug Safety*, 17, S101-S102 available from: WOS:000258420100232

Dunnell, K. 2007. The changing demographic picture of the UK: national statistician's annual article on the population. *Population Trends*, 130, 9-21

Eaton, L. Europeans and Americans turn to internet for health information. British Medical Journal 325, 989. 2002.
Ref Type: Journal (Full)

Edwards, I. & Aronson, J. 2000. Adverse drug reactions: definitions, diagnosis, and management. *The Lancet*, 356, 1255-1259

Elliott, W.J. 2008. What Factors Contribute to the Inadequate Control of Elevated Blood Pressure? *Journal of Clinical Hypertension*, 10, (1) 20-26 available from: WOS:000261306800004

Eysenbach, G. & Wyatt, J. 2002. Using the Internet for Surveys and Health Research. *Journal of Medical Internet Research*, 4, (2) available from: ISI:000207624800008

Farmer, A., Bruckner-Holt, C., Cook, M., & Hearing, S. 2009. Social networking sites: a novel portal for communication. *Postgraduate Medical Journal*, 85, (1007) 455-459

Faye, O. & Roujeau, J.C. 2005. Treatment of epidermal necrolysis with high-dose intravenous immunoglobulins (IVIg) - Clinical experience to date. *Drugs*, 65, (15) 2085-2090 available from: WOS:000233360400002

Fellahi, A., Zouhair, K., Amraoui, A., & Benchikhi, H. 2011. Stevens-Johnson and Lyell syndromes: Mucocutaneous and ocular sequels in 43 cases. *Annales de Dermatologie et de Venereologie*, 138, (2) 88-92 available from: WOS:000288624700003

Ferner, R.E. & Aronson, J.K. 2010. Preventability of Drug-Related Harms - Part I A Systematic Review. *Drug Safety*, 33, (11) 985-994 available from: WOS:000283613900003

Fick, D.M., Cooper, J.W., Wade, W.E., Waller, J.L., Maclean, J.R., & Beers, M.H. 2003. Updating the beers criteria for potentially inappropriate medication use in older adults - Results of a US consensus panel of experts. *Archives of Internal Medicine*, 163, (22) 2716-2724 available from: WOS:000187007700007

Field, T.S., Gilman, B.H., Subramanian, S., Fuller, J.C., Bates, D.W., & Gurwitz, J.H. 2005. The costs associated with adverse drug events among older adults in the ambulatory setting. *Medical Care*, 43, (12) 1171-1176 available from: WOS:000233711100003

Finkelstein, Y., Soon, G.S., Acuna, P., George, M., Pope, E., Ito, S., Shear, N.H., Koren, G., Shannon, M.W., & Garcia-Bournissen, F. 2011. Recurrence and Outcomes of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Children. *Pediatrics*, 128, (4) 723-728 available from: WOS:000295406800049

Fisher, S. & Bryant, S.G. 1990. Postmarketing Surveillance - Accuracy of Patient Drug Attribution Judgments. *Clinical Pharmacology & Therapeutics*, 48, (1) 102-107 available from: WOS:A1990DR01000013

Franceschi, M., Scarcelli, C., Niro, V., Seripa, D., Pazienza, A.M., Pepe, G., Colusso, A.M., Pacilli, L., & Pilotto, A. 2008. Prevalence, clinical features and avoidability of adverse drug reactions as cause of admission to a Geriatric Unit - A prospective study of 1756 patients. *Drug Safety*, 31, (6) 545-556 available from: WOS:000256758200009

French, L.E. 2006. Toxic Epidermal Necrolysis and Steven Johnson Syndrome: Our Current Understanding. *Allergology*, 55, 9-16

Fromowitz, J.S., Ramos-Caro, F.A., & Flowers, F.P. 2007. Practical guidelines for the management of toxic epidermal necrolysis and Stevens-Johnson syndrome. *International Journal of Dermatology*, 46, (10) 1092-1094 available from: WOS:000249883200020

Frost, J.H. & Massagli, M.P. 2008. Social Uses of Personal Health Information Within PatientsLikeMe, an Online Patient Community: What Can Happen When Patients Have Access to One Another's Data. *Journal of Medical Internet Research*, 10, (3) available from: ISI:000263213500004

Gallagher, P., Ryan, C., Byrne, S., Kennedy, J., & O'Mahony, D. 2008. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert Doctors to Right Treatment). Consensus validation. *International Journal of Clinical Pharmacology and Therapeutics*, 46, (2) 72-83 available from: WOS:000253357100003

Gallagher, P.F., O'Connor, M.N., & O'Mahony, D. 2011. Prevention of Potentially Inappropriate Prescribing for Elderly Patients: A Randomized Controlled Trial Using STOPP/START Criteria. *Clinical Pharmacology & Therapeutics*, 89, (6) 845-854 available from: WOS:000290786000024

Garcia-Doval, I., LeCleach, L., Bocquet, H., Otero, X.L., & Roujeau, J.C. 2000. Toxic epidermal necrolysis and Stevens-Johnson syndrome - Does early withdrawal of causative drugs decrease the risk of death? *Archives of Dermatology*, 136, (3) 323-327 available from: WOS:000085879900006

Gerull, R., Nelle, M., & Schaible, T. 2011. Toxic epidermal necrolysis and Stevens-Johnson syndrome: A review. *Critical Care Medicine*, 39, (6) 1521-1532 available from: WOS:000290715000041

Gholami, K. & Shalviri, G. 1999. Factors associated with preventability, predictability, and severity of adverse drug reactions. *Annals of Pharmacotherapy*, 33, (2) 236-240 available from: WOS:000078931700016

Ginsberg, G., Hattis, D., Russ, A., & Sonawane, B. 2005. Pharmacokinetic and pharmacodynamic factors that can affect sensitivity to neurotoxic sequelae in elderly individuals. *Environmental Health Perspectives*, 113, (9) 1243-1249 available from: WOS:000231677700048

Goh, L.Y., Vitry, A.I., Semple, S.J., Esterman, A., & Luszcz, M.A. 2009. Self-medication with over-the-counter drugs and complementary medications in South Australia's elderly population. *Bmc Complementary and Alternative Medicine*, 9, available from: WOS:000271859900001

Gonzalez-Heydrich, J., Bromley, D., Strohecker, C., Marks, J., Demaso, D.R., Ackermann, E., Gibson, S., Shen, C., & Umaschi, M. 1998. *Experience journals: Using computers to share personal stories about illness and medical intervention*.

Goyder, C., McPherson, A., & Glasziou, P. 2009. Diagnosis in General Practice Self diagnosis. *British Medical Journal*, 339, available from: WOS:000271833900002

Greenblatt, D.J., Shader, R.I., & Harmatz, J.S. 1989. Implications of Altered Drug Disposition in the Elderly - Studies of Benzodiazepines. *Journal of Clinical Pharmacology*, 29, (10) 866-872 available from: WOS:A1989CA00900002

Greenhalgh, T. & Hurwitz , B. 1999. Why study narrative? *British Medical Journal*, 318, 48-50Accessed 25 February 2011.

Guardiola-Wanden-Berghe, R., Gil-Perez, J.D., Sanz-Valero, J., & Wanden-Berghe, C. 2011. Evaluating the quality of websites relating to diet and eating disorders. *Health Information and Libraries Journal*, 28, (4) 294-301 available from: WOS:000297244600007

Gueudry, J., Roujeau, J.C., Binaghi, M., Soubrane, G., & Muraine, M. 2009. Risk Factors for the Development of Ocular Complications of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. *Archives of Dermatology*, 145, (2) 157-162 available from: WOS:000263380000006

Gueyffier, F., Bulpitt, C., Boissel, J.P., Schron, E., Ekbom, T., Fagard, R., Casiglia, E., Kerlikowske, A., & Coope, J. 1999. Antihypertensive drugs in very old people: a subgroup meta-analysis of randomised controlled trials. *Lancet*, 353, (9155) 793-796 available from: WOS:000079089100010

Gurwitz, J.H. & Avorn, J. 1991. The Ambiguous Relation Between Aging and Adverse Drug-Reactions. *Annals of Internal Medicine*, 114, (11) 956-966 available from: WOS:A1991FM97900008

Gurwitz, J.H., Field, T.S., Avorn, J., McCormick, D., Jain, S., Eckler, M., Benser, M., Edmondson, A.C., & Bates, D.W. 2000. Incidence and preventability of adverse drug events in nursing homes. *American Journal of Medicine*, 109, (2) 87-94 available from: WOS:000088922800001

Hakkarainen, K.M., Andersson Sundell, K., Petzold, M., & Hagg, S. 2012. Methods for assessing the preventability of adverse drug events: a systematic review. *Drug safety : an*

international journal of medical toxicology and drug experience, 35, (2) 105-126 available from: MEDLINE:22201475

Halevy, S., Ghislain, P.D., Mockenhaupt, M., Fagot, J.P.E., Bavinck, J.N.B., Sidoroff, A., Naldi, L., Dunant, A., Viboud, C., & Roujeau, J.C. 2008. Allopurinol is the most common cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe and Israel. *Journal of the American Academy of Dermatology*, 58, (1) 25-32 available from: WOS:000252287400002

Hall, J., Peat, M., Birks, Y., Golder, S., Entwistle, V., Gilbody, S., Mansell, P., McCaughan, D., Sheldon, T., Watt, I., Williams, B., & Wright, J. 2010. Effectiveness of interventions designed to promote patient involvement to enhance safety: a systematic review. *Quality & Safety in Health Care*, 19, (5) available from: WOS:000285032700030

Hallas, J., Harvald, B., Gram, L.F., Grodum, E., Brosen, K., Haghfelt, T., & Damsbo, N. 1990. Drug Related Hospital Admissions - the Role of Definitions and Intensity of Data-Collection, and the Possibility of Prevention. *Journal of Internal Medicine*, 228, (2) 83-90 available from: WOS:A1990DU68600003

Hamilton, H., Gallagher, P., Ryan, C., Byrne, S., & O'Mahony, D. 2011. Potentially Inappropriate Medications Defined by STOPP Criteria and the Risk of Adverse Drug Events in Older Hospitalized Patients. *Archives of Internal Medicine*, 171, (11) 1013-1019

Hamilton, H., Gallagher, P., & O'Mahony, D. 2009. Inappropriate prescribing and adverse drug events in older people. *BMC Geriatrics*, 9, (5) doi:10.1186/1471-2318-9-5

Hanlon, J.T., Schmader, K.E., Samsa, G.P., Weinberger, M., Uttech, K.M., Lewis, I.K., Cohen, H.J., & Feussner, J.R. 1992. A Method for Assessing Drug-Therapy Appropriateness. *Journal of Clinical Epidemiology*, 45, (10) 1045-1051 available from: WOS:A1992JR93200001

Hardey, M. 2002. 'The story of my illness': personal accounts of illness on the Internet. *Health*, 6, (1) 31-46 available from: ISI:000173530500002

Hardey, M. 2010. 'E-health': the internet and the transformation of patients into consumers and producers of health knowledge. *Information, Communication & Society*, 4, (3) 388-405

Harr, T. & French, L.E. 2010. Toxic epidermal necrolysis and Stevens-Johnson syndrome. *Orphanet Journal of Rare Diseases*, 5, available from: WOS:000286073100001

Hart, R., Minto C, & Creighton S. Vaginal adhesions caused by Stevens-Johnson Syndrome. Journal of Pediatric and Adolescent Gynecology 15[3], 151-152. 2002.
Ref Type: Journal (Full)

Hartholt, K.A., van der Velde, N., Looman, C.W.N., Panneman, M.J.M., Van Beeck, E.F., Patka, P., & van der Cammen, T.J.M. 2010. Adverse Drug Reactions Related Hospital Admissions in Persons Aged 60 Years and over, The Netherlands, 1981-2007: Less Rapid Increase, Different Drugs. *Plos One*, 5, (11) available from: WOS:000284147700022

Hazell, L. & Shakir, S.A.W. 2006. Under-reporting of adverse drug reactions - A systematic review. *Drug Safety*, 29, (5) 385-396 available from: WOS:000237955700003

Herxheimer, A., McPherson, A., Miller, R., Shepperd, S., Yaphe, J., & Ziebland, S. 2000. Database of patients' experiences (DIPEx): a multi-media approach to sharing experiences and information. *Lancet*, 355, (9214) 1540-1543 available from: ISI:000086830100041

Hoffler, D. & Morgenstern, H.O. 1990. Age Dependence of Therapy Result and Risk in the Treatment of Arterial-Hypertension. *Journal of Cardiovascular Pharmacology*, 16, S184-S188 available from: WOS:A1990EW26400033

Howard, R.L., Avery, A.J., Slavenburg, S., Royal, S., Pipe, G., Lucassen, P., & Pirmohamed, M. 2007. Which drugs cause preventable admissions to hospital? A systematic review. *British Journal of Clinical Pharmacology*, 63, (2) 136-147 available from: WOS:000243376600002

Hunziker, T., Kunzi, U.P., Braunschweig, S., Zehnder, D., & Hoigne, R. 1997. Comprehensive hospital drug monitoring (CHDM): Adverse skin reactions, a 20-year survey. *Allergy*, 52, (4) 388-393 available from: WOS:A1997XA22100007

Ipsos MORI & MHRA 2006, *Risks and Benefits of Medicines and Medical Devices- Perceptions, communication & Regulation. Overview of Ipsos MORI Research Conducted for The Medicines and Healthcare products Regulatory Agency.*

Jarernsiripornkul, N., Kakaew, W., Loalukkana, W., & Krska, J. 2009. Adverse drug reaction monitoring: comparing doctor and patient reporting for new drugs. *Pharmacoepidemiology and Drug Safety*, 18, (3) 240-245 available from: WOS:000264371300008

Jarernsiripornkul, N., Krska, J., Capps, P.A.G., Richards, R.M.E., & Lee, A. 2002. Patient reporting of potential adverse drug reactions: a methodological study. *British Journal of Clinical Pharmacology*, 53, (3) 318-325 available from: WOS:000174370000014

Java, A., Song, X., Finin, T., & Tseng, B. 2009. Why We Twitter: An analysis of a Microblogging Community. *Advances in Web Mining and Web Usage Analysis*, 5439, 118-138

Jick, T.D. 1979. Mixing Qualitative and Quantitative Methods - Triangulation in Action. *Administrative Science Quarterly*, 24, (4) 602-611 available from: WOS:A1979HX29300009

Kelemen, J.J., Cioffi, W.G., Mcmanus, W.F., Mason, A.D., & Pruitt, B.A. 1995. Burn Center Care for Patients with Toxic Epidermal Necrolysis. *Journal of the American College of Surgeons*, 180, (3) 273-278 available from: WOS:A1995QK36300002

Khazaal, Y., Chatton, A., Cochand, S., Coquard, O., Fernandez, S., Khan, R., & Zullino, D. 2010. Quality of web-based information on alcohol dependence. *Drugs-Education Prevention and Policy*, 17, (3) 248-260 available from: WOS:000277388500005

Kim, S. 2009. Content analysis of cancer blog posts. *Journal of the Medical Library Association*, 97, (4) 260-266 available from: ISI:000273820300010

Kim, S.H., Lee, K.W., Song, W.J., Kim, S.H., Jee, Y.K., Lee, S.M., Kang, H.R., Park, H.W., Cho, S.H., Park, S.H., Min, K.U., & Chang, Y.S. 2011. Carbamazepine-induced severe cutaneous adverse reactions and HLA genotypes in Koreans. *Epilepsy Research*, 97, (1-2) 190-197 available from: WOS:000297873800022

Kinnane, N. & Milne, D. 2010. The role of the internet in supporting and informing carers of people with cancer: a literature review. *Support Care Cancer*, 18, (9) 1123-1136

Knezevic, M.Z., Bivolarevic, I.C., Peric, T.S., & Jankovic, S.M. 2011. Using Facebook to Increase Spontaneous Reporting of Adverse Drug Reactions. *Drug Safety*, 34, (4) 351-352 available from: WOS:000289539700009

Kratzert, K., Marks, F., Antoine, C., Brescia, R.J., Parodneck, L., & Young, B.K. 1988. Pregnancy Post-Stevens-Johnson Syndrome - Case-Report and Review of the Literature. *Obstetrics and Gynecology*, 72, (3) 447-450 available from: WOS:A1988P852300005

Langer, R.D., Ganiats, T.G., & Barrettconnor, E. 1989. Paradoxical Survival of Elderly Men with High Blood-Pressure. *British Medical Journal*, 298, (6684) 1356-1357 available from: WOS:A1989U736200019

Langille, M., Bernard, A., Rodgers, C., Hughes, S., Leddin, D., & van Zanten, S.V. 2010. Systematic Review of the Quality of Patient Information on the Internet Regarding Inflammatory Bowel Disease Treatments. *Clinical Gastroenterology and Hepatology*, 8, (4) 322-328 available from: WOS:000276784700007

Laroche, M.L., Charmes, J.P., Nouaille, Y., Picard, N., & Merle, L. 2007. Is inappropriate medication use a major cause of adverse drug reactions in the elderly? *British Journal of Clinical Pharmacology*, 63, (2) 177-186 available from: WOS:000243376600008

Lau, D.T., Kasper, J.D., Potter, D.E.B., Lyles, A., & Bennett, R.G. 2005. Hospitalization and death associated with potentially inappropriate medication prescriptions among elderly nursing home residents. *Archives of Internal Medicine*, 165, (1) 68-74 available from: WOS:000226219800009

Lazarou, J., Pomeranz, B.H., & Corey, P.N. 1998. Incidence of adverse drug reactions in hospitalized patients - A meta-analysis of prospective studies. *Jama-Journal of the American Medical Association*, 279, (15) 1200-1205 available from: WOS:000072969400034

Leosco, D., Pisani, E., Testa, G., De Santis, D., Carnovale, V., Abete, P., Ferrara, N., Beneduce, F., & Rengo, F. 2002. Advances in treatment strategies of hypertension in elderly subjects: Very low dose combination in first line. *Archives of Gerontology and Geriatrics* 171-179 available from: WOS:000202846600022

Lin, C.F., Wang, C.Y., & Bai, C.H. 2011. Polypharmacy, Aging and Potential Drug-Drug Interactions in Outpatients in Taiwan A Retrospective Computerized Screening Study. *Drugs & Aging*, 28, (3) 219-225

Lindblad, C.I., Hanlon, J.T., Gross, C.R., Sloane, R.J., Pieper, C.F., Hajjar, E.R., Ruby, C.M., & Schmader, K.E. 2006. Clinically important drug-disease interactions and their

prevalence in older adults. *Clinical Therapeutics*, 28, (8) 1133-1143 available from: WOS:000240521000006

Lopez-Jornet, P. & Camacho-Alonso, F. 2009. The quality of internet sites providing information relating to oral cancer. *Oral Oncology*, 45, (9) E95-E98 available from: WOS:000269326700005

Lopez-Jornet, P. & Camacho-Alonso, F. 2010a. The quality of internet information relating to oral leukoplakia. *Medicina Oral Patologia Oral y Cirugia Bucal*, 15, (5) E727-E731 available from: WOS:000281778900011

Lopez-Jornet, P. & Camacho-Alonso, F. 2010b. The quality of patient-orientated Internet information on oral lichen planus: a pilot study. *Journal of Evaluation in Clinical Practice*, 16, (5) 883-886 available from: WOS:000281897100003

Lowry, K.P., Dudley, T.K., Oddone, E.Z., & Bosworth, H.B. 2005. Intentional and unintentional nonadherence to anti hypertensive medication. *Annals of Pharmacotherapy*, 39, (7-8) 1198-1203 available from: WOS:000230229400007

Lyell, A. 1956. Toxic Epidermal Necrolysis - An Eruption Resembling Scalding of the Skin. *British Journal of Dermatology*, 68, (11) 355-361 available from: WOS:A1956XL82800003

Lyubomirsky, S., Sousa, L., & Dickerhoof, R. 2006. The costs and benefits of writing, talking, and thinking about life's triumphs and defeats. *Journal of Personality and Social Psychology*, 90, (4) 692-708 available from: WOS:000237370500012

Macedo, A.F., Alves, C., Craveiro, N., & Marques, F.B. 2011. Multiple drug exposure as a risk factor for the seriousness of adverse drug reactions. *Journal of Nursing Management*, 19, (3) 395-399 available from: WOS:000289737500014

Mallet, L., Spinewine, A., & Huang, A. 2007. Prescribing in elderly people 2 - The challenge of managing drug interactions in elderly people. *Lancet*, 370, (9582) 185-191 available from: WOS:000248091600033

Mancia, G., Bertineri, G., & Grassi, G. 1983. Effects of blood pressure measured by the doctor on patient's blood pressure and heart rate. *Lancet*, 2, 695-698

Mannesse, C.K., Derkx, F.H.M., de Ridder, M.A.J., 'T Veld, A.J.M.I., & van der Cammen, T.J.M. 2000. Contribution of adverse drug reactions to hospital admission of older patients. *Age and Ageing*, 29, (1) 35-39 available from: WOS:000084906600009

Mannesse, C.K., Derkx, F.H.M., deRidder, M.A.J., MainintVeld, A.J., & vanderCammen, T.J.M. 1997. Adverse drug reactions in elderly patients as contributing factor for hospital admission: cross sectional study. *British Medical Journal*, 315, (7115) 1057-1058 available from: WOS:A1997YD44500023

Martin, U. & Coleman, J. 2007, "Drugs and the Elderly," *In Pharmacovigilance*, Second ed. R. Mann & E. Andrews, eds., West Sussex: Wiley, pp. 515-532.

Martin, U., Hill, C., & O'Mahony, D. 2005. Use of moxonidine in elderly patients with resistant hypertension. *Journal of Clinical Pharmacy and Therapeutics*, 30, (5) 433-437 available from: WOS:000231677200004

Mason, O. Linguistic analysis program. 2009. Department of English, University of Birmingham.
Ref Type: Computer Program

Masoodi, N. 2008. Polypharmacy: To err is human, to correct divine. *British Journal of Medical Practitioners*, 1, (1) 6-9

Mattila, K., Haavisto, M., Rajala, S., & Heikinheimo, R. 1988. Blood-Pressure and 5-Year Survival in the Very Old. *British Medical Journal*, 296, (6626) 887-889 available from: WOS:A1988M785100008

Maume, D. Gender differences in providing urgent childcare among dual-earner parents. Social Forces 87[1], 273-297. 2008.
Ref Type: Journal (Full)

Mcgee, T. & Munster, A. 1998. Toxic epidermal necrolysis syndrome: Mortality rate reduced with early referral to Regional Burn Center. *Plastic and Reconstructive Surgery*, 102, (4) 1018-1022 available from: WOS:000075711300014

Mclean, A.J. & Le Couteur, D.G. 2004. Aging biology and geriatric clinical pharmacology. *Pharmacological Reviews*, 56, (2) 163-184 available from: WOS:000222021100001

Meneux, E., Wolkenstein, P., Haddad, B., Roujeau, J.C., Revuz, J., & Paniel, B.J. 1998. Vulvovaginal involvement in toxic epidermal necrolysis: A retrospective study of 40 cases. *Obstetrics and Gynecology*, 91, (2) 283-287 available from: WOS:000071670800023

Mets, T.F. 1995. Drug-Induced Orthostatic Hypotension in Older Patients. *Drugs & Aging*, 6, (3) 219-228 available from: WOS:A1995QK20600005

Miller, E. & Pole, A. Diagnosis Blog: Checking up on health Blogs in the Blogosphere. Research and Practice 100[8], 1514-1519. 2010.
Ref Type: Journal (Full)

Mino-Leon, D., Reyes-Morales, H., Galvan-Plata, M.E., Ponce-Monter, H., Palma-Aguirre, J.A., Amato, D., & Figueras, A. 2007. Drug treatment of hypertension: compliance and adverse reactions in a cohort of hypertensive patients in a primary care setting. *Revista de Investigacion Clinica*, 59, (1) 8-14 available from: WOS:000246503500002

Mo, P.K.H. & Coulson, N.S. 2008. Exploring the communication of social support within virtual communities: A content analysis of messages posted to an online HIV/AIDS support group. *Cyberpsychology & Behavior*, 11, (3) 371-374 available from: ISI:000257319900020

Mo, P.K.H. & Coulson, N.S. 2010. Living with HIV/AIDS and Use of Online Support Groups. *Journal of Health Psychology*, 15, (3) 339-350 available from: ISI:000276031500003

Mockenhaupt, M. 2009. Severe drug-induced skin reactions: clinical pattern, diagnostics and therapy. *Journal der Deutschen Dermatologischen Gesellschaft*, 7, (2) 142-160 available from: WOS:000265141300009

Morgan, T.O., Anderson, A., & Jones, E. 1992. Comparison and Interaction of Low-Dose Felodipine and Enalapril in the Treatment of Essential-Hypertension in Elderly Subjects. *American Journal of Hypertension*, 5, (4) 238-243 available from: WOS:A1992HP87600006

Moride, Y., Haramburu, F., Requejo, A.A., & Begaud, B. 1997. Under-reporting of adverse drug reactions in general practice. *British Journal of Clinical Pharmacology*, 43, (2) 177-181 available from: WOS:A1997WJ54600007

Muhlberg, W. & Platt, D. 1999. Age-dependent changes of the kidneys: Pharmacological implications. *Gerontology*, 45, (5) 243-253 available from: WOS:000082417700001

Nair, B. 2002. Evidence based medicine for older people: available, accessible, acceptable, adaptable? *Australasian Journal on Ageing*, 21, (2) 58-60

Naldi, L., Conforti, A., Venegoni, M., Troncon, M.G., Caputi, A., Ghiotto, E., Cocci, A., Moretti, U., Velo, G., & Leone, R. 1999. Cutaneous reactions to drugs. An analysis of spontaneous reports in four Italian regions. *British Journal of Clinical Pharmacology*, 48, (6) 839-846 available from: WOS:000084103600008

Nassif, A., Bensussan, A., Boumsell, L., Deniaud, A., Moslehi, H., Wolkenstein, P., Bagot, M., & Roujeau, J.C. 2004. Toxic epidermal necrolysis: Effector cells are drug-specific cytotoxic T cells. *Journal of Allergy and Clinical Immunology*, 114, (5) 1209-1215 available from: WOS:000225047800032

Nguyen, J.K., Fouts, M.M., & Kotabe, S.E. 2002. Is polypharmacy a risk factor for adverse drug reaction in geriatric nursing home residents? *Journal of the American Geriatrics Society*, 50, (4) S83 available from: WOS:000175030500262

Ni Riordain, R. & McCreary, C. 2009. Head and neck cancer information on the internet: Type, accuracy and content. *Oral Oncology*, 45, (8) 675-677 available from: WOS:000268112800006

NICE 2011, *Hypertension: Clinical management of primary hypertension in adults*.

O'Brien, M.R. & Clark, D. 2010. Use of unsolicited first-person written illness narratives in research: systematic review. *Journal of Advanced Nursing*, 66, (8) 1671-1682 available from: ISI:000279447100003

O'Mahony, D., Gallagher, P., Ryan, C., Byrne, S., Hamilton, H., Barry, P., O'Connor, M., & Kennedy, J. 2010. STOPP & START criteria: A new approach to detecting potentially inappropriate prescribing in old age. *European Geriatric Medicine*, 1, (1) 45-51 available from: WOS:000287640500010

Oates, D.J., Berlowitz, D.R., Glickman, M.E., Silliman, R.A., & Borzecki, A.M. 2007. Blood pressure and survival in the oldest old. *Journal of the American Geriatrics Society*, 55, (3) 383-388 available from: WOS:000244519400009

Office of National Statistics 2010,
Statistical Bulletin: Internet Access 2010, Households and Individuals.

Olivier, P., Bertrand, L., Tubery, M., Lauque, D., Montastruc, J., & Lapeyre-Mestre 2009. Hospitalizations because of Adverse Drug Reactions in Elderly Patients Admitted through the Emergency Department. *Drugs & Aging*, 26, (6) 475-482

Onder, G., Pedone, C., Landi, F., Cesari, M., Della Vedova, C., Bernabei, R., & Gambassi, G. 2002. Adverse drug reactions as cause of hospital admissions: Results from the Italian Group of Pharmacoepidemiology in the Elderly (GIFA). *Journal of the American Geriatrics Society*, 50, (12) 1962-1968 available from: WOS:000179747400007

Oplatek, A., Brown, K., Sen, S., Halerz, M., Supple, K., & Gamelli, R.L. 2006. Long-term follow-up of patients treated for toxic epidermal Necrolysis. *Journal of Burn Care & Research*, 27, (1) 26-33 available from: WOS:000237697600005

Overberg, R., Otten W, de Man A, Toussaint P, Westenbrink J, & Zwetsloot-Schonk B 2010. How breast cancer patients want to search for and retrieve information from stories of other patients on the internet: an online randomised controlled experiment. *Journal of Medical Internet Research*, 12, (1)

Oxford University Press. http://oxforddictionaries.com/definition/narrative. 2012. 23-2-2012.
Ref Type: Online Source

Page, R. & Ruscin, J. 2006. The risk of adverse drug events and hospital-related morbidity and mortality among older adults with potentially inappropriate medication use. *The American Journal of Geriatric Pharmacotherapy*, 4, (4) 297-305

Paquet, P., Jacob, E., Damas, P., & Pierard, G.E. 2002. Recurrent fatal drug-induced toxic epidermal necrolysis (Lyell's syndrome) after putative beta-lactam cross-reactivity: Case report and scrutiny of antibiotic imputability. *Critical Care Medicine*, 30, (11) 2580-2583 available from: WOS:000179322900028

Patterson, D., Carrigan, L., & Questad, K. 1990. Post-traumatic stress disorder in hospitalized patients with burns injuries. *J Burn Care Rehabil*, 11, (3) 181-184

Pennebaker, J.W. 1997. Writing about emotional experiences as a therapeutic process. *Psychological Science*, 8, (3) 162-166 available from: WOS:A1997WZ23900007

Pennebaker, J.W. & Seagal, J.D. 1999. Forming a story: The health benefits of narrative. *Journal of Clinical Psychology*, 55, (10) 1243-1254 available from: WOS:000082857500006

Perri, M., Menon, A.M., Deshpande, A.D., Shinde, S.B., Jiang, R., Cooper, J.W., Cook, C.L., Griffin, S.C., & Lorys, R.A. 2005. Adverse outcomes associated with inappropriate drug use in nursing homes. *Annals of Pharmacotherapy*, 39, (3) 405-411 available from: WOS:000227102500001

Pickering, G. 2004. Frail elderly, nutritional status and drugs. *Archives of Gerontology and Geriatrics*, 38, (2) 174-180 available from: WOS:000188510400009

Pirmohamed, M., James, S., Meakin, S., Green, C., Scott, A.K., Walley, T.J., Farrar, K., Park, B.K., & Breckenridge, A.M. 2004. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18,820 patients. *British Medical Journal*, 329, (7456) 15-19 available from: WOS:000222568300015

Prisant, L.M. 2002. Fixed low-dose combination in first-line treatment of hypertension. *Journal of Hypertension*, 20, S11-S19 available from: WOS:000174460800003

Puig, J.G., Calvo, C., Luurila, O., Luurila, H., Sulosaari, S., Strandberg, A., & Ghezzi, C. 2007. Lercanidipine, enalapril and their combination in the treatment of elderly hypertensive patients: placebo-controlled, randomized, crossover study with four ABPM. *Journal of Human Hypertension*, 21, (12) 917-924 available from: WOS:000251139400003

Raine, J. 2011. An analysis of successful litigation claims in children in England . *Archives of Disease in Childhood*, 96 , (9) 838-840

Rajakaruna, G. & Butt, T. 2007. Drug-induced acute kidney injury. *Adverse Drug Reaction Bulletin* (245) 939-942

Rawlins, M.D. 1988. Spontaneous Reporting of Adverse Drug-Reactions .1. the Data. *British Journal of Clinical Pharmacology*, 26, (1) 1-5 available from: WOS:A1988P135200001

Rawlins, M. D. & Thompson, J. 1977, "Pathogenesis of adverse drug reactions," *In Textbook of adverse drug reactions*, D. Davies, ed., Oxford: Oxford University Press.

Robinson, K. 2001.
Unsolicited narratives from the internet: A rich source of qualitative data. *Qualitative Health Research*, 11, (5) 706-714

Rochon, P.A. & Gurwitz, J.H. 1997. Optimising drug treatment for elderly people: the prescribing cascade. *British Medical Journal*, 315, (7115) 1096-1099 available from: WOS:A1997YD44500036

Roujeau, J.C. & Bastuji-Garin, S. 2011. Systematic review of treatments for Stevens-Johnson syndrome and toxic epidermal necrolysis using the SCORTEN score as a tool for evaluating mortality. *Therapeutic Advances in Drug Safety*, 2, (3) 87-94

Roujeau, J.C., Guillaume, J.C., Fabre, J.P., Penso, D., Flechet, M.L., & Girre, J.P. 1990. Toxic Epidermal Necrolysis (Lyell Syndrome) - Incidence and Drug Etiology in France, 1981-1985. *Archives of Dermatology*, 126, (1) 37-42 available from: WOS:A1990CH25800003

Roujeau, J.C., Kelly, J.P., Naldi, L., Rzany, B., Stern, R.S., Anderson, T., Auquier, A., Bastujigarin, S., Correia, O., Locati, F., Mockenhaupt, M., Paoletti, C., Shapiro, S., Shear, N., Schopf, E., & Kaufman, D.W. 1995. Medication Use and the Risk of Stevens-Johnson Syndrome Or Toxic Epidermal Necrolysis. *New England Journal of Medicine*, 333, (24) 1600-1607 available from: WOS:A1995TK06500004

Roujeau, J.C. & Stern, R.S. 1994. Severe Adverse Cutaneous Reactions to Drugs. *New England Journal of Medicine*, 331, (19) 1272-1285 available from: WOS:A1994PP75200006

Routledge, P.A., O'Mahony, M.S., & Woodhouse, K.W. 2004. Adverse drug reactions in elderly patients. *British Journal of Clinical Pharmacology*, 57, (2) 121-126 available from: WOS:000188507300002

Rozmovits, L. & Ziebland, S. 2004. What do patients with prostate or breast cancer want from an Internet site? A qualitative study of information needs. *Patient Education and Counseling*, 53, (1) 57-64 available from: ISI:000221136300009

Saiag, P., Caumes, E., Chosidow, O., Revuz, J., & Roujeau, J.C. 1992. Drug-Induced Toxic Epidermal Necrolysis (Lyell Syndrome) in Patients Infected with the Human-Immunodeficiency-Virus. *Journal of the American Academy of Dermatology*, 26, (4) 567-574 available from: WOS:A1992HL54100009

Salzman, C. 2005. *Clinical Geriatric Psychopharmacology*, Fourth ed. Lippincott Williams & Wilkins.

Satish, S., Freeman, D.H., Ray, L., & Goodwin, J.S. 2001. The relationship between blood pressure and mortality in the oldest old. *Journal of the American Geriatrics Society*, 49, (4) 367-374 available from: WOS:000168331300003

Schneck, J., Fagot, J.P., Sekula, P., Sassolas, B., Roujeau, J.C., & Mockenhaupt, M. 2008. Effects of treatments on the mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis: A retrospective study on patients included in the prospective EuroSCAR study. *Journal of the American Academy of Dermatology*, 58, (1) 33-40 available from: WOS:000252287400003

Schopf, E., Stuhmer, A., Rzany, B., Victor, N., Zentgraf, R., & Kapp, J.F. 1991. Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome - An Epidemiologic-Study from West-Germany. *Archives of Dermatology*, 127, (6) 839-842 available from: WOS:A1991FQ35000006

Schumock, G.T. & Thornton, J.P. 1992. Focusing on the preventability of adverse drug reactions . *Hospital Pharmacy*, 26, (6) 538

Schwartz, J.B. 1996. Calcium antagonists in the elderly - A risk-benefit analysis. *Drugs & Aging*, 9, (1) 24-36 available from: WOS:A1996UW62600003

Secoli, S.R., Figueras, A., Lebrao, M.L., de Lima, F.D., & Santos, J.L.F. 2010. Risk of Potential Drug-Drug Interactions among Brazilian Elderly A Population-Based, Cross-Sectional Study. *Drugs & Aging*, 27, (9) 759-770 available from: WOS:000282468000006

SHEP cooperative Research Group 1991. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic blood hypertension. Final results of the Systolic in the Elderly Program (SHEP). *Jama-Journal of the American Medical Association*, 265, (24) 3255-3264

Shi, S.J. & Klotz, U. 2011. Age-Related Changes in Pharmacokinetics. *Current Drug Metabolism*, 12, (7) 601-610 available from: WOS:000295405400002

Shiyanbola, O.O. & Farris, K.B. 2010. Concerns and Beliefs About Medicines and Inappropriate Medications: An Internet-Based Survey on Risk Factors for Self-Reported Adverse Drug Events Among Older Adults. *American Journal of Geriatric Pharmacotherapy*, 8, (3) 245-257 available from: WOS:000279578200006

Somkrua, R., Eickman, E.E., Saokaew, S., Lohitnavy, M., & Chaiyakunapruk, N. 2011. Association of HLA-B*5801 allele and allopurinol-induced stevens johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. *Bmc Medical Genetics*, 12, available from: WOS:000295778400001

Spinewine, A., Schmader, K.E., Barber, N., Hughes, C., Lapane, K.L., Swine, C., & Hanlon, J.T. 2007. Prescribing in elderly people 1 - Appropriate prescribing in elderly people: how well can it be measured and optimised? *Lancet*, 370, (9582) 173-184 available from: WOS:000248091600032

Staessen, J.A., Byttebier, G., Buntinx, F., Celis, H., Obrien, E.T., & Fagard, R. 1997a. Antihypertensive treatment based on conventional or ambulatory blood pressure measurement - A randomized controlled trial. *Jama-Journal of the American Medical Association*, 278, (13) 1065-1072 available from: WOS:A1997XX30300029

Staessen, J.A., Fagard, R., Thijs, L., Celis, H., Arabidze, G.G., Birkenhager, W.H., Bulpitt, C.J., deLeeuw, P.W., Dollery, C.T., Fletcher, A.E., Forette, F., Leonetti, G., Nachev, C., Obrien, E.T., Rosenfeld, J., Rodicio, J.L., Tuomilehto, J., & Zanchetti, A. 1997b. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet*, 350, (9080) 757-764 available from: WOS:A1997XW28200009

Staessen, J.A., Thijs, L., Fagard, R., O'Brien, E.T., Clement, D., de Leeuw, P.W., Mancia, G., Nachev, C., Palatini, P., Parati, G., Tuomilehto, J., & Webster, J. 1999. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. *Jama-Journal of the American Medical Association*, 282, (6) 539-546 available from: WOS:000081919100027

Stevens, A.M. & Johnson, F.C. 1922. A new eruptive fever associated with stomatitis and ophthalmia - Report of two cases in children. *American Journal of Diseases of Children*, 24, (6) 526-533 available from: WOS:000201725500005

Strauss, A. & Corbin, J. 1990. *Basics of Qualitative research. Grounded Theory Procedures and Techniques.*, First ed. London, Sage Publications.

Struck, M.F., Hilbert, P., Mockenhaupt, M., Reichelt, B., & Steen, M. 2010. Severe cutaneous adverse reactions: emergency approach to non-burn epidermolytic syndromes. *Intensive Care Medicine*, 36, (1) 22-32 available from: WOS:000273683300005

Taylor, J.O., Cornonihuntley, J., Curb, J.D., Manton, K.G., Ostfeld, A.M., Scherr, P., & Wallace, R.B. 1991. Blood-Pressure and Mortality Risk in the Elderly. *American Journal of Epidemiology*, 134, (5) 489-501 available from: WOS:A1991GH06500009

Taylor, S.E., Falke, R.L., Shoptaw, S.J., & Lichtman, R.R. 1986. Social Support, Support Groups, and the Cancer-Patient. *Journal of Consulting and Clinical Psychology*, 54, (5) 608-615 available from: ISI:A1986E297200004

Teo, L., Tay, Y.K., Liu, T.T., & Kwok, C. 2009. Stevens-Johnson syndrome and toxic epidermal necrolysis: efficacy of intravenous immunoglobulin and a review of treatment options. *Singapore Medical Journal*, 50, (1) 29-33 available from: WOS:000263938400007

Thurmond, V.A. 2001. The point of triangulation. *Journal of Nursing Scholarship*, 33, (3) 253-258 available from: WOS:000171988400015

Tomlinson, B. 1996. Optimal dosage of ACE inhibitors in older patients. *Drugs & Aging*, 9, (4) 262-273 available from: WOS:A1996VL78500004

Trifiro, G. & Spina, E. 2011. Age-related Changes in Pharmacodynamics: Focus on Drugs Acting on Central Nervous and Cardiovascular Systems. *Current Drug Metabolism*, 12, (7) 611-620 available from: WOS:000295405400003

van der Marel, S., Duijvestein, M., Hardwick, J.C., van den Brink, G.R., Veenendaal, R., Hommes, D.W., & Fidder, H.H. 2009. Quality of Web-based Information on Inflammatory Bowel Diseases. *Inflammatory Bowel Diseases*, 15, (12) 1891-1896 available from: WOS:000272568600018

van Grootheest, K., de Graaf, L., & de Jong-van den Berg, L. 2003. Consumer adverse drug reaction reporting - A new step in pharmacovigilance? *Drug Safety*, 26, (4) 211-217 available from: WOS:000181811500001

van Grootheest, K. & de Jong-van den Berg, L. 2004. Patients' role in reporting adverse drug reactions. *Expert Opinion on Drug Safety*, 3, (4) 363-368 available from: MEDLINE:15268652

Veehof, L.J.G., Stewart, R.E., Meyboom-de Jong, B., & Haaijer-Ruskamp, F.M. 1999. Adverse drug reactions and polypharmacy in the elderly in general practice. *European Journal of Clinical Pharmacology*, 55, (7) 533-536 available from: WOS:000082848500008

Verdecchia, P., Staessen, J.A., White, W.B., Imai, Y., & O'Brien, E.T. 2002. Properly defining white coat hypertension. *European Heart Journal*, 23, (2) 106-109 available from: WOS:000173390100006

WHO 1972. International Drug Monitoring the Role of National Centers Report of A Who Meeting Geneva Switzerland September 20-25 1971. *WHO Technical Report Series*, 498, 5-47 available from: BCI:BCI197208085257

WHO Collaborating Centre for International Drug Monitoring 1992, *International monitoring of adverse reactions to drugs: adverse reaction terminology.* Uppsala, Sweden.

Wicks, P., Massagli, M., Frost, J., Brownstein, C., Okun, S., Vaughan, T., Bradley, R., & Heywood, J. 2010. Sharing Health Data for Better Outcomes on PatientsLikeMe. *Journal of Medical Internet Research*, 12, (2) available from: ISI:000278860800009

Wicks, P.J., Frost, J., Massagli, M.P., & Heywood, J. 2008. Online data-sharing community for patients with Parkinson's disease: PatientsLikeMe.com. *Movement Disorders*, 23, (1) 1017 available from: ISI:000256393801408

Williams, B., Poulter, N.R., Brown, M.J., Davis, M., McInnes, G.T., Potter, J.F., Sever, P.S., & Thom, S.M. 2004. Guidelines for management of hypertension: Report of the fourth working party of the British Hypertension Society, 2004 - BHSIV. *Journal of Human Hypertension*, 18, (3) 139-185 available from: WOS:000189035700001

Wilson, E.E. & Malinak, L.R. 1988. Vulvovaginal Sequelae of Stevens-Johnson Syndrome and Their Management. *Obstetrics and Gynecology*, 71, (3) 478-480 available from: WOS:A1988M457300017

Wing, L.M.H., Brown, M.A., Beilin, L.J., Ryan, P., & Reid, C.M. 2002. 'Reverse white-coat hypertension' in older hypertensives. *Journal of Hypertension*, 20, (4) 639-644 available from: WOS:000174960500020

World Health Organisation. The importance of Pharmacovigilance: Safety Monitoring of Medicinal Products. 2002. Geneva, WHO.
Ref Type: Pamphlet

Ziebland, S., Chapple, A., Dumelow, C., Evans, D., Prinjha, S., & Rozmovits, L. 2004. How the internet affects patients' experience of cancer: a qualitative study. *British Medical Journal*, 328, (7439) 564-+ available from: ISI:000220091800025

6 APPENDICES

Appendices A–D related to Chapter 2. The appendices also contain two of the papers I published based upon work presented in this thesis. They are representations of the original papers and are therefore not labelled, or numbered consecutively as per the remainder of this thesis.

APPENDIX A

Participant Invitation Letter (Version 2: 13/02/09)

13th February 2009

Dear Mr. _____

Please allow me to introduce myself. I am a Skin Specialist (Consultant Dermatologist) working at Selly Oak Hospital, and I am currently conducting a medical research study in collaboration with other researchers at the University of Birmingham, involving talking to patients who have been admitted to hospital with serious skin conditions.

According to our hospital dermatology records, I understand that you have been admitted to hospital in the past with a skin condition, and it is likely that I may have been involved in treating your condition at some point during your hospital stay**.** I therefore wondered if you would be kind enough to consider taking part in our research.

The study would involve talking to you (for around 40 minutes), about your past experiences of the condition, either at home, at the hospital, or another appropriate venue. There are no right or wrong answers and all your views are helpful to us.

Your discussion with us will be completely confidential and anonymous; that is, your name or personal details will not be attached to any data that we obtain through talking to you.

Please find enclosed an information sheet about the study.

If you feel that you may be able to take part, I would be grateful if you could complete the enclosed slip, and return it the pre-paid envelope provided. Alternatively you can ring my co-researcher, Dr Tehreem Butt on either 0121 6272582 or 07800 937748, or email her at t.f.butt@bham.ac.uk if you require more information.

If you are happy for us to contact you by telephone, we will give you a ring in a fortnight's time to explain the study in more detail.

Many thanks for your help, and look forward to hearing from you!

Yours sincerely

Dr Helen Lewis MBChB MRCP
Consultant Dermatologist
University Hospital Birmingham NHS Trust & University of Birmingham

APPENDIX B

Reply slip for Selly Oak & City Hospital Skin study (Version1: 12/12/08)

Name_____

Contact phone number_____

I will / will not be willing to consider taking part in the study
(Please circle appropriate response)

Please tick this box if you are happy to be contacted by telephone ☐

Please insert into enclosed pre-paid envelope and post!

Many thanks for your time!

APPENDIX C

Consent form (Version 1: 12/12/08)

Participant Reference Number for this study: _____

Title of Project: Patient experiences and perceptions of serious skin conditions and views on medications

Name of Chief Researcher: Dr Tehreem F Butt

Please initial each box

1. I confirm that I have read and understood the patient information sheet dated…13/02/2009 (Version 2) for the above study and have had the opportunity to ask questions. ☐
2. I understand my participation is voluntary and that I am free to withdraw at any time, without giving any reason. ☐
3. I agree to the audio-recording of the interview. ☐
4. I would be happy for the chief researcher to cross-check my hospital medical records to confirm relevant medical details related to my hospital admission. ☐
5. I agree for my GP to be informed about my participation in the study. ☐
6. I agree to take part in the above study. ☐

Name of participant _____

Signature _____

Date _____

Researcher Dr. Tehreem Butt

Signature _____

Date _____

APPENDIX D

School of Medicine
Division of Medical Sciences

Department of Clinical Pharmacology,
The Medical School,
Edgbaston,
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Lecturer and Specialist registrar

Dr Tehreem F Butt MBChB MRCP

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UNIVERSITY OF BIRMINGHAM

Participant Information Sheet

Title of study: Experiences of patients with serious skin conditions and views towards medications

Version: 2 (13/02/2009)

Researchers: Dr Tehreem Butt, Dr Anthony Cox, Dr. Helen Lewis and Professor Robin Ferner

You have been invited to take part in a research study. Before you decide whether you want to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. If there is anything that is unclear, please ask for further information.

Purpose of the study

We are looking to explore the experiences of people who have been admitted to hospital with serious skin conditions, and to talk to them about their experiences during their hospital stay and how their condition has affected them. This will help us better understand the condition from the 'patient's perspective', and help us improve the management of such patients in the future.

Why have I been chosen?

You have been asked to take part because according to our hospital records you have been admitted to Selly Oak Hospital/ Queen Elizabeth hospital or City Hospital in the past with a skin condition requiring emergency treatment.

Do I have to take part?

It is up to you to decide whether or not you wish to take part. If you do decide to take part, you will be asked to sign a consent form, a copy of which you may keep. If you decide to take part, you are still free to withdraw at any time during the interview, without giving a reason. You can also withdraw at any time after the interview by placing a phone call to the chief researcher (Dr Tehreem Butt) with your unique reference code.

What will happen to me if I take part?

If you agree to take part, we would like to talk to you for approximately 40 minutes about the experiences of your skin condition related to your admission to hospital.

There are no right or wrong answers and all your views are helpful to us. We would like to audio-record this conversation so that what you have said can be accurately noted, but if you are uncomfortable with this, written notes can be taken as you talk instead.

Everything you say will be confidential and anonymous – that is, your name or personal details won't be attached to it in any way, so you will not be identifiable later. Only your unique reference code will be associated with the recording and subsequent notes. Recordings will be destroyed after transcription of the interview.

Support during the interview

Individuals usually find it beneficial to talk about their experiences, even though they may be have been upsetting. Sometimes, however, people may find talking about their experiences upsetting, and if you find that this is the case during the interview, we are trained to provide any support and reassurance required. We can also provide information about support groups and counselling services which are available, who you may contact for further support. Remember, if at any time you feel unable to continue, we can stop the interview immediately, and you can withdraw from the study if you wish.

What do I have to do?

If you decide to take part in this research, we would first like you to sign a consent form to confirm you have read this information sheet and understand the aims of this research.

The interview will be performed at venue of your choice; you may prefer to be interviewed at the hospital where you have been seen previously, or in the comfort of your own home; if you choose to be interviewed at the hospital, we will reimburse you for any travel expenses incurred. The interview should not take longer than 40 minutes. It may take less time if you do not wish to say

much, but can take longer if you wish. The duration of the interview is up to you.

When we have finished asking questions, you will be offered the chance to listen to the recording of the interview. If you are not happy to let us take the recording away with us, you will be offered the chance to either take the recording away with you, or we can erase the recording before we leave.

However, if you are happy with us to keep the recording, you will then be given a unique and confidential reference code which will be documented on this information sheet alongside the date the interview was conducted. Should you decide you do not want to take part in this study within a week of the interview, all you have to do is contact us either by telephone or email, stating your reference code and the tape recording of your interview will be destroyed.

Cross-checking medical records

We may also need to cross-check your hospital medical records to confirm relevant medical details related to your hospital admission, but will only do so with your permission.

After the study

You can let us know if you would like to be informed of the findings of the study once they are available, by contacting us at the email address or contact telephone number above (printed on the right hand corner of this letter).

APPENDIX E

SJS Study interview schedule (V1: Jan 2009)

Participant name_____ Ref no_____

Date of interview_____

INTRODUCTION

Firstly, would thank you for agreeing to take part in our study. I will ask you a series of questions, and would be grateful if you were as open and honest as possible; remember, there are no right or wrong answers!

PATIENT EXPERIENCES, KNOWLEDGE, AND UNDERSTANDING

- The letter we sent you mentioned a skin condition our records say that you have experienced; (are you aware of this event) and could you tell me a little more about it/what happened?
- Do you know the formal/ medical name of the condition?
- What do you believe caused this skin condition?
- (If not sure, provide a list of possible causes including drugs, infections, no cause etc)
- What were you told about the condition? Including the cause of the condition. What information were you given at the time, and when?
- How did you feel when you were given this information?
- Can you remember your experiences in the hospital? If so, could you tell me about them and what happened?
- Would you describe your experiences as predominantly positive or negative, and why?
- How has your experience affected your life physically?
- How has your experience affected your life psychologically/ how if at all, has the experience of your hospital admission and the condition affected your psychological well being?

- Do you think your experience has changed your outlook on life?
- Had you ever heard of the condition (Steven Johnson syndrome or Toxic Epidermal Necrolysis) before developing the condition?

FOR PATIENTS WHO BELIEVE THAT THE EVENT WAS DRUG- RELATED

- What were you taking this drug for?
- Had you been warned that this skin reaction was a possible side-effect of the drug you were taking?
- Do you think that this skin reaction is common or relatively rare?
- Are you aware if your doctor reported the reaction to anybody?

If not warned prior to reaction

- Do you think you should have been warned? (Bearing in mind that it is a very rare condition)
- Would you still have taken the drug if you had been warned?

If warned prior to reaction

- You say you were warned about the potential risk of this reaction, how did you decide to take the drug?

Patients views on safety of culprit drug

What are your views on the safety of the drug that caused your reaction?

- Do you think your views on medicines have changed after your reaction?

PATIENTS VIEWS ON SAFETY OF DRUGS IN GENERAL, CURRENT AND FUTURE MEDICATION USE

- What do you think about the safety of medicines in general?
- How do think people should be told about the risks of medicines?

- Do you currently take any prescription medicines or have you taken any in the past?

- Do you currently take any OTC medicines or have you taken any in the past?

- Do you currently take any herbal or homeopathic products or have you taken any in the past?

- If you do take or have taken medicines, what are your thoughts on the risks and benefits associated with these?

- Where do you find information about medicines?

- Who do you trust as sources of information on medicines?

- What are your views on medicine information sources and do you think that they are adequate?

- If you had side effect to a medicine, would you tell anyone about it, and if so, who?

- Where you aware that you can report side- effects yourself? How do you feel about that?

- How do you think the risks associated with medicines should be communicated to the public?

Journal of Human Hypertension (2010), 1–5

www.nature.com/jhh

ORIGINAL ARTICLE

Managing hypertension in the very elderly: effect of adverse drug reactions (ADRs) on achieving targets

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The Hypertension in the Very Elderly trial (HYVET), demonstrated the benefit of antihypertensive treatment in patients ⩾80 years. However, patients in this age group are at increased risk of drug interactions and adverse effects. We conducted a retrospective cohort study, in hypertensive patients aged ⩾80 years, to determine whether it is possible to follow the HYVET guidelines in an everyday clinical setting. We identified 100 patients aged ⩾80 years referred to the Hypertension Clinic, University Hospital Birmingham, over a 10-year period. Most patients were referred to the clinic because of poorly controlled blood pressure despite treatment and all had 24 h ambulatory blood pressure monitoring (ABPM) as part of their assessment. All patients tolerated ABPM, and a 'white coat' effect was demonstrated in 33 patients. In 64 out of 100 patients (57 on treatment), the ABPM confirmed poor blood pressure control. Despite this, 26 of these patients had an antihypertensive either stopped (15), and /or reduced (3) or left unchanged (9) at clinic because of documented adverse drug reactions (ADRs). In 36 out of 100 patients, no additional antihypertensive therapy was needed because the blood pressure was either well-controlled on treatment (28), over-treated (4), or normotensive with a white coat effect (4). Despite this, antihypertensive agents were either stopped (10), and or reduced (5) because of ADRs in half the patients (14) from the well-controlled group. In conclusion, 40% patients had documented ADRs overall which limited further intervention, suggesting that implementation of the HYVET recommendations in clinical practice may be difficult.
Journal of Human Hypertension advance online publication, 4 February 2010; doi:10.1038/jhh.2009.116

Keywords: elderly; ABPM; adverse drug reactions (ADRs)

Introduction

The population in the United Kingdom is ageing. In 1981 just 1% of the population was aged 85 years and over, but in the last 25 years the number has doubled to 1.2 million and is expected to further increase to 2.9 million by 2031. A total of 4% of the UK population will then be 85 years or more.[1]

As the population ages, more patients are expected to develop chronic age-related conditions such as hypertension. At present, it is estimated that more than 50% of the 12 million people in the UK over 60 years are hypertensive, even when a relatively high threshold (⩾160/95 mm Hg) is used for diagnosis.[2] Until recently, it was unclear whether the treatment of very elderly hypertensive patients, that is, those of 80 years or more, conferred more benefit than risk. Many trials in the past have either excluded such patients, or have recruited too few to show benefit of treatment. A subgroup meta-analysis of randomized trials suggested that treatment of hypertension in this group resulted in a 36% reduction in stroke but an increased risk of death from any cause.[3] A further retrospective cohort study demonstrated lower survival rates in patients in their eighties with systolic blood pressures of <140 mm Hg on antihypertensive treatment.[4]

The findings of the Hypertension in the Very Elderly trial (HYVET), however, have led to a re-evaluation of the clinical management of hypertension in this group of patients.[5] This double-blind, placebo-controlled multi-centre trial, randomly assigned 3845 patients aged 80 years and above, with a sustained systolic blood pressure of ⩾160 mm Hg to indapamide (sustained release 1.5 mg, with or without perindopril) or placebo, to achieve a target blood pressure of 150/80 mm Hg. Treatment was associated with a 30% reduction in fatal or non-fatal stroke

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(95% confidence interval (CI)−1–50, $P=0.06$), a 21% reduction in the mortality rate from any cause (95% CI, 4–35, $P=0.02$), a 23% reduction in the rate of death from cardiovascular disease (95% CI, −1–40, $P=0.06$), and a 64% reduction in the rate of heart failure (95% CI, 42–78, $P=0.001$). Of note, there were fewer reported adverse events in the treatment group.

These findings support the hypothesis that treatment of hypertension should include the very elderly at least to a target blood pressure of 150/80 mm Hg, but this may pose difficulties in practice. Older people with hypertension often have several other co-existing medical conditions, for which they may be taking multiple medications. This increases the risk of drug interactions and adverse effects with antihypertensives. Increasing age is also associated with changes in pharmacokinetics and pharmacodynamics, impaired cardiac, renal and baroreceptor function, and cognitive impairment, all of which can make prescribing in this age group challenging.[6–8]

The aim of this study was to determine whether development of or the potential risk of adverse drug reactions (ADRs) to antihypertensive drugs limits the clinician's ability to follow guidelines and achieve blood pressure targets in the very elderly. Ambulatory blood pressure monitoring (ABPM) was used to assess blood pressure control at the time of referral to a hospital hypertension service. We then assessed whether the presence of ADRs limited our ability to act on the results of the ABPM to improve control.

Materials and methods

We conducted a retrospective cohort study to identify hypertensive patients aged 80 years or over who had attended the Hypertension Research Clinic, Wellcome Clinical Research Facility, University Hospital Birmingham over a 10-year period. This clinic runs as a part of the Hypertension Service and deals with 500 new referrals per year. All patients have ambulatory blood pressure monitoring carried out as a part of the routine clinical service.

Patients were identified either from a database of hypertensive patients attending the clinic (Microsoft Access 2002), or from clinic letters and medical records dating from 1998 when the clinic was set up. For the purpose of this study the following data were extracted for patients aged 80 years or over: reason for referral to the hypertension clinic, clinic blood pressure readings, mean daytime and nighttime 24 h ABPM readings, current antihypertensive medications, clinical diagnosis and changes in medications or recommendations on management made after the clinic appointment.

On the basis of the ambulatory blood pressure monitoring data all patients were categorized according to the thresholds and targets used in the HYVET study. The mean daytime blood pressure was the principle parameter used to categorize blood pressure. An adjustment upward of 10 mm Hg systolic and 5 mm Hg diastolic was made to the mean daytime readings to allow for the differences in home and office readings in accordance with British Hypertension Society Guidelines.[3] Thus, in unmedicated patients a diagnosis of hypertension was made if the mean daytime ABPM systolic reading was $\geqslant$150 mm Hg. This corresponded with the threshold of 160 mm Hg used in the HYVET study. Patients who were already on treatment at the time of the clinic referral were considered to have well-controlled blood pressure if their mean day time ABPM was $<$140/75 mm Hg or poorly controlled blood pressure if it was $\geqslant$140/75 mm Hg. This corresponds to the target of 150/80 mm Hg used in the HYVET study. For those patients whose blood pressure was higher at night, the mean nighttime pressures were used for analysis. For the purposes of the analysis taking the HYVET targets into account, unmedicated patients were considered to have 'white coat' hypertension if the mean ambulatory blood pressure was $<$140/75 mm Hg but the first few readings (or clinic readings) were $>$150 mm Hg. Patients on antihypertensive treatment were considered to be over medicated if the mean day time systolic pressure was $<$130 mm Hg systolic.

Results

We identified a sample of 100 patients who were aged 80 years or over at the time of referral, between April 1998 and May 2008. A small number of patients were excluded because of missing data. The age range was 80–94 years, with a mean age of 83 years. The commonest reason for referral to the hypertension clinic was 'difficult to control hypertension'.

The diagnostic codes assigned to patients based on their mean daytime ABPM readings are outlined in Figure 1. Most (64 out of 100) patients were diagnosed with 'poorly controlled blood pressure' on the basis of ABPM (mean daytime pressure $\geqslant$140/75 mm Hg). This was despite the treatment in 57 patients. A total of 6 unmedicated patients were found to have confirmed hypertension and 1 patient was unmedicated, despite having poorly controlled BP, owing to adverse effects.

Of the 64 'poorly controlled patients', 38 patients were appropriately started on an additional antihypertensive according to the British Hypertension Society guidelines[3] or had the dose of an existing antihypertensive increased. In 17 additional patients an additional agent was added to reduce the blood pressure, but one (or more) of their existing hypertensives were either stopped or the dose reduced, predominantly as a result of ADRs. Eight

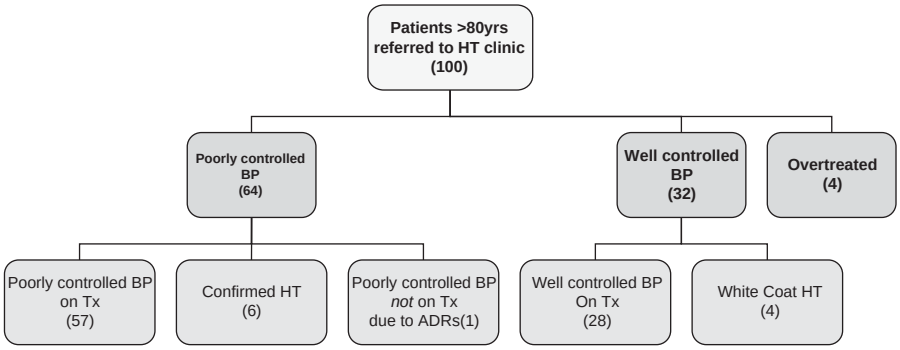

Figure 1 Diagnoses at clinic based on mean daytime ABPM reading.

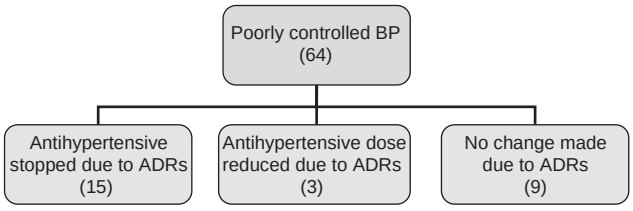

Figure 2 Influence of ADRs on management of patients with poorly controlled blood pressure.

patients had no change made to their medications despite poor control because previous ADRs precluded further intervention (Figure 2), in addition one confirmed hypertensive remained unmedicated because of ADRs. Some problems limiting treatment options in this group included ankle oedema secondary to amlodipine, adverse effects secondary to beta-adrenoceptor blockers, and large variability in blood pressure on ABPM, increasing the risk of hypotensive episodes with addition of further therapy (Table 1). Finally, 12 patients in the poorly controlled group had a marked 'white coat' effect identified on the ABPM, which would have led to aggressive escalation of therapy if surgery and/or clinic readings were used to guide management.

An additional 36 of 100 patients, who were on antihypertensive medication at the time of referral to clinic, did not warrant any further intervention as the blood pressure was well-controlled (28 patients) or too tightly controlled (4 patients) on ambulatory monitoring.

A 'white coat' effect was identified in 17 of these patients. Furthermore, four unmedicated patients were diagnosed with 'white coat' hypertension and did not need treatment (Figure 1). Of the 28 elderly patients, whose blood pressure was well-controlled on treatment, 13 had no change made to their treatment. Half of the patients from this group (14 out of 28), however, had an antihypertensive agent stopped and/or reduced owing to ADRs, despite good blood-pressure control (Figure 3). Reported ADRs included ankle oedema (calcium-channel blockers), headache (ACE inhibitor), cold extremities and bradycardia (beta-adrenoceptor blockers),

Table 1 Adverse drug reactions (ADRs) documented in patients of 80 years or over with poorly controlled blood pressure on ambulatory blood pressure monitoring (ABPM)

Antihypertensive agent	*ADRs/reasons for stopping, reducing dose or limiting treatment options*
Beta-adrenoceptor blockers (3) Atenolol Bisoprolol	First degree heart block (1), fatigue (2)
Thiazide diuretics (4) Bendroflumathiazide	'Intolerant' (1), hyponatraemia (2) and development of type 2 diabetes (1)
Calcium-channel antagonists (5) Amlodipine Diltiazem Verapamil	Ankle oedema (3), bradycardia (1) and 'reacted badly' (1)
Alpha blockers (2) Doxazosin	Urinary frequency (1), oedema (1)
Centrally acting agents (1) Moxonidine	'Intolerant' (1)
ACE-inhibitors (1) Enalapril	'Intolerant' (1)

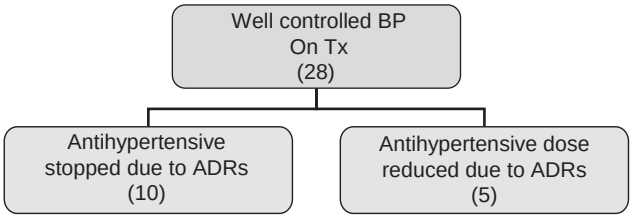

Figure 3 Influence of ADRs on management of patients with well-controlled blood pressure.

hyponatremia (ARBs), and worsening renal function (ARB, ACE-inhibitor and thiazide diuretics) (Table 2). Seven patients, who had an antihypertensive agent stopped, were started on an alternative agent in its place. The four patients who had low blood pressure on ABPM had an antihypertensive agent stopped to avoid postural symptoms.

Table 2 Adverse drug reactions (ADRs) documented in elderly patients with well-controlled blood pressure on ambulatory blood pressure monitoring (ABPM)

Antihypertensive agent	*ADRs/reasons for stopping, reducing dose or limiting treatment options*
Beta-adrenoceptor blockers (3) Atenolol	Cold extremities (1), 'intolerant' (1), fatigue and dyspnoea (1)
Thiazide diuretics (1) Bendroflumathiazide	Constipation (1)
Loop/potassium-sparing diuretic (1) Co-amilofruse	Renal impairment (1)
Calcium-channel antagonists (2) Diltiazem	Constipation (1), ankle oedema (1)
Alpha blockers (2) Doxazosin	Muscle cramps (1), rhinitis (1)
Centrally acting agents (1) Moxonidine	'Symptomatic' (1)
ACE-inhibitors/ARBs (5) Telmisartan Losartan Ramipril Candesartan Lisinopril	Hyponatraemia (1), 'intolerant' (1), headache (1) and renal impairment (2)

Discussion

This study highlights the difficulties of treating patients of 80 years and over with antihypertensives even when the target blood pressure is relatively modest (150 mm Hg). Almost half the patients had documented ADRs, which limited further intervention (40 out of 100) or had very low blood pressure that necessitated withdrawal of therapy (4 patients) to avoid troublesome postural symptoms. The results suggest that aggressive treatment of hypertension in the very elderly may be difficult to achieve in practice, because of the high incidence of ADRs and poor tolerability of drugs in this age group.

There are several reasons why older people may be more vulnerable to adverse drug reactions including age-related changes in pharmacokinetics and pharmacodynamics, impaired cardiac, renal and baroreceptor function, and cognitive impairment.[6–8] Several studies have confirmed the high incidence of ADRs in elderly patients taking antihypertensives, and these agents are a frequent cause of ADRs leading to hospital admission.[9,10] Polypharmacy is common in the elderly and can increase the risk of drug interactions and adverse events as a consequence. The prevalence of postural or orthostatic hypotension has been reported to be between 10 and 30% for elderly people and is particularly associated with the use of antihypertensive medication.[11] Reduced renal clearance of various drugs including antihypertensives, can increase plasma levels and thus increase the risk of toxicity.[12] Poor compliance with antihypertensive therapy can also be a problem in managing elderly patients with hypertension. Non compliance with drug therapy is reported to occur in around 30–50% of elderly patients.[13] A number of factors can contribute to poor compliance, including poor communication with healthcare professionals, decline in cognitive or physical function and complicated dosage regimens.

The HYVET study provided compelling evidence that hypertension treatment based on indapamide with or without perindopril in the very elderly aiming for a target of 150/80 mm Hg is beneficial. Active treatment was associated with impressive reductions in stroke rates, deaths from any cause and heart failure. There was a very low incidence of trial medication-related adverse events.[1] In our study of patients of 80 years or over attending a hospital-based hypertension clinic; however, problems with ADRs were common and in many cases limited the ability to treat to target.

Our findings also demonstrated that diagnoses based on office readings in the community rather than average day time ambulatory readings, would have led to inappropriate escalation of medication in a significant proportion of our elderly patients, many of whom had a marked 'white coat' effect. This confirms how useful 24 h ABPM can be, even in the very elderly, who tolerated the procedure surprisingly well. The use of ABPM in the diagnosis and monitoring of hypertension has increased in recent years and has led to improvements in blood pressure measurement. In addition, ABPM has been shown to be a better predictor of cardiovascular mortality and end organ damage and is the only way to identify 'non-dippers'.[14] Our findings are in keeping with the Second Australian National Blood Pressure Study, which showed that the mean daytime ABPM readings were lower than clinic readings in a large cohort of untreated elderly hypertensives, although a substantial proportion also showed a reverse 'white coat' effect.[15] Further results from the HYVET study in relation to cardiovascular outcomes and ambulatory data in the very elderly are awaited.[16]

Conclusion

In conclusion, our study highlights the challenge of prescribing antihypertensive medication in very elderly patients and suggests that a high incidence of ADRs may preclude treatment to a target of 150 mm Hg. It also suggests that ambulatory monitoring may have a role in managing these patients, particularly for individuals experiencing difficulties with their medication. The study is limited by the fact that the patients included were attending a hospital

clinic because of poorly controlled blood pressure, so may not be representative of very elderly patients managed in primary care. Nonetheless, the findings suggest that careful monitoring of very elderly patients taking antihypertensive agents is needed.

What is known about this topic

- Findings of the Hypertension in the Very Elderly trial (HYVET) study suggest that hypertension in the very elderly (aged 80 years and over) should be treated to at least a target blood pressure of 150/80 mm Hg.
- Several other studies, however, report a high incidence of adverse drug reactions (ADRs) in elderly patients taking antihypertensives, frequently leading to hospital admission.

What this study adds

- This retrospective cohort study of elderly patients aged 80 years and over suggests that implementing the HYVET recommendations in clinical practice is challenging because of the high incidence of ADRs in this age group.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

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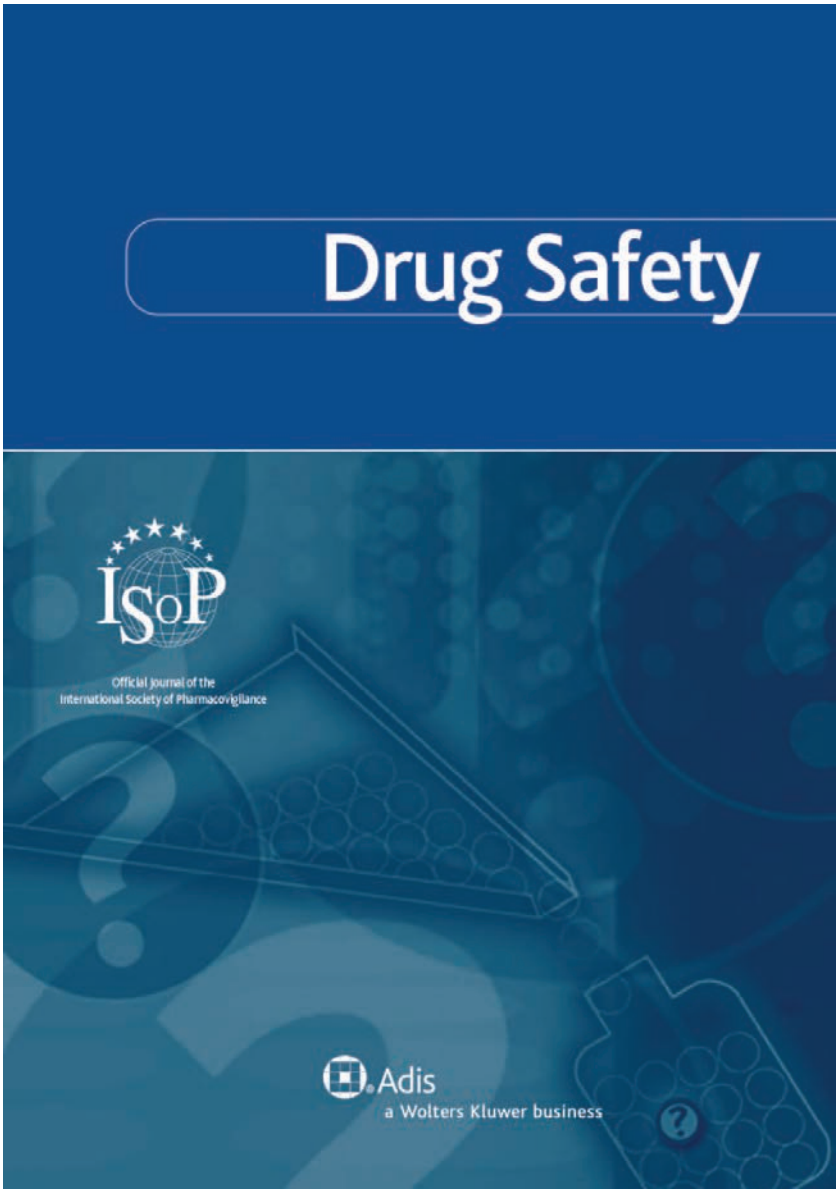
References

1 Dunnell K. The changing demographic picture of the UK: national statistician's annual article on the population. *Popul Trends* 2007; **130**: 9–21.
2 Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF *et al.* Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004-BHS IV. *J Hum Hypertens* 2004; **18**(3): 139–185.
3 Gueyffier F, Bulpitt C, Boissel JP, Schron E, Ekbom T, Fagard R *et al.* Antihypertensive drugs in very old people: a subgroup meta-analysis of randomised controlled trials. INDANA Group. *Lancet* 1999; **353**(9155): 793–796.
4 Oates DJ, Berlowitz DR, Glickman ME, Silliman RA, Borzecki AM. Blood pressure and survival in the oldest old. *J Am Geriatr Soc* 2007; **55**(3): 383–388.
5 Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D *et al.* Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 2008; **358**(18): 1887–1898.
6 Kostis JB. Treating hypertension in the very old. *N Engl J Med* 2008; **358**(18): 1958–1960.
7 Milton JC, Hill-Smith I, Jackson SH. Prescribing for older people. *BMJ* 2008; **336**(7644): 606–609.
8 Mallet L, Spinewine A, Huang A. The challenge of managing drug interactions in elderly people. *Lancet* 2007; **370**(9582): 185–191.
9 Williamson J, Chopin JM. Adverse reactions to prescribed drugs in the elderly: a multicentre investigation. *Age Ageing* 1980; **9**: 73–80.
10 Mann R, Andrews E. *Pharmacovigilance*, 2nd edn. John Wiley and sons Ltd: England, UK, 2007.
11 Mets TF. Drug-induced orthostatic hypotension in older patients. *Drugs Ageing* 1995; **6**(3): 219–228.
12 Salzman C. *Clinical Geriatric Psychopharmacology*, 4th edn. Lippincott Williams & Wilkins: Philadelphia, PA, USA, 2005.
13 Morrow D, Leirer V, Sheikh J. Adherence and medication instructions review and recommendations. *J Am Geriatr Soc* 1988; **36**(12): 1147–1160.
14 Chavanu K, Merkel J, Quan AM. Role of ambulatory blood pressure monitoring in the management of hypertension. *Am J Health Syst Pharm* 2008; **65**(3): 209–218.
15 Wing LM, Brown MA, Beilin LJ, Ryan P, Reid CM. ANBP2 Management Committee and Investigators. Second Australian National Blood Pressure Study. *J Hypertens* 2002; **20**(4): 639–644.
16 Pinto E, Bulpitt C, Beckett N, Peters R, Staessen JA, Rajkumar C. Rationale and methodology of monitoring ambulatory blood pressure and arterial compliance in the Hypertension in the Very Elderly Trial. *Blood Press Monit* 2006; **11**(1): 3–8.



ORIGINAL RESEARCH ARTICLE

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Patient Experiences of Serious Adverse Drug Reactions and Their Attitudes to Medicines

A Qualitative Study of Survivors of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in the UK

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Abstract

Background: Adverse drug reactions (ADRs) cause significant morbidity and mortality and account for around 6.5% of hospital admissions. Patient experiences of serious ADRs and their long-term impact on patients' lives, including their influence on current attitudes towards medicines, have not been previously explored.

Objective: The aim of the study was to explore the experiences, beliefs, and attitudes of survivors of serious ADRs, using drug-induced Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) as a paradigm.

Methods: A retrospective, qualitative study was undertaken using detailed semi-structured interviews. Fourteen adult survivors of SJS and TEN, admitted to two teaching hospitals in the UK, one the location of a tertiary burns centre, were interviewed. Interview transcripts were independently analysed by three different researchers and themes emerging from the text identified.

Results: All 14 patients were aware that their condition was drug induced, and all but one knew the specific drug(s) implicated. Several expressed surprise at the perceived lack of awareness of the ADR amongst healthcare professionals, and described how the ADR was mistaken for another condition.

Survivors believed that causes of the ADR included (i) being given too high a dose of the drug; (ii) medical staff ignoring existing allergies; and (iii) failure to monitor blood tests. Only two believed that the reaction was unavoidable. Those who believed that the condition could have been avoided had less trust in healthcare professionals. The ADR had a persisting impact on their current lives physically and psychologically. Many now avoided medicines altogether and were fearful of becoming ill enough to need them.

Conclusions: Life-threatening ADRs continued to affect patients' lives long after the event. Patients' beliefs regarding the cause of the ADR differed, and may have influenced their trust in healthcare professionals and medicines. We propose that clear communication during the acute phase of a serious ADR may therefore be important.

Background

Approximately 6.5% of hospital admissions in the UK are related to ADRs, with an associated mortality of 0.15%, costing the National Health Service £466 million annually.[1]

Drug-induced Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are rare but serious and acutely life-threatening cutaneous adverse drug reactions (ADRs). SJS and TEN are considered to be part of a single spectrum of disease; SJS affects <10% of body surface area (BSA), with a mortality rate of 1–5%, whereas TEN affects >30% of BSA, with a higher mortality rate of 30–40%. Cases involving between 10% and 30% of BSA are classed as SJS-TEN overlap syndrome.[2,3]

Although over 100 drugs have been implicated, a limited number of drugs, including sulfonamides, anticonvulsant agents, and allopurinol, are most consistently associated with SJS and TEN.[4] Thought to be immune-complex-mediated hypersensitivity disorders, they are characterized by epidermal necrosis, leading to extensive epidermal detachment, mucous membrane erosion and severe constitutional symptoms.[5] The complications of SJS and TEN are similar to those of extensive burns, and survivors of SJS and TEN may therefore suffer lasting morbidity that impairs their quality of life.

Despite their impact on patient morbidity and mortality, the experiences of patients who have suffered the effects of serious ADRs such as SJS and TEN have not been previously explored. We present the findings of a novel retrospective study of adult survivors of SJS and TEN. In order to generate hypotheses regarding experiences of serious ADRs, we explore their experiences and understanding of the condition, and how these influenced their current attitudes towards medicines and ADRs.

Methods

We employed a qualitative approach derived from grounded theory due to the exploratory nature of the study. Our aim was to generate new hypotheses regarding patients' experiences and beliefs about serious ADRs such as SJS and TEN rather than to test them.[6]

We identified survivors of SJS and TEN, aged 18 years and over, admitted over a 10-year period to one of two teaching hospitals in Birmingham, UK. One hospital contained a specialist burns unit, which admitted patients with the condition, and a number of patients had therefore been transferred from other hospitals in the UK.

As SJS and TEN are very rare (estimated annual incidence of 1–2 per million population) and are associated with a high mortality rate, purposive sampling was not feasible.

Patients were identified either from an existing dermatology database of patients diagnosed with drug-induced SJS and TEN, or from medical records through diagnostic codes assigned to them. Forty-eight survivors were identified and contacted by letter, and 18 agreed to participate in the study. Of these, four were excluded: one died from an unrelated condition, two were subsequently uncontactable and one patient had no recollection of being diagnosed or admitted to hospital with the condition. Participants were contacted by telephone to arrange interviews.

Twenty-eight patients did not respond to the invitation to participate and two patients formally declined. Of those who either declined or did not respond, 19 (63%) were female and 11 were male; age range was 20–89 years (mean 46.8 years).

Data Collection

Semi-structured interviews of patients were undertaken using a standardized interview topic

guide devised by TFB, ARC and REF. Patients were interviewed independently by TFB (ten) and ARC (four). All interviews were either conducted at the hospital or at the patient's home, depending on patient preference, and were audio-recorded with the patient's permission. Open questions were asked regarding their experiences of the condition and the circumstances surrounding it, their beliefs regarding the cause or precipitant of the adverse event and their views towards medicines. Patients were encouraged to openly express their own views with minimal intervention from the interviewer. The interview topic guide evolved as interviews progressed, and a final version was developed after the fifth interview (see Supplemental Digital Content 1, http://links.adisonline.com/DSZ/A40, for full interview topic guide).

Analysis

Audio recordings of interviews were transcribed and analysed using an approach based on grounded theory and using the qualitative software package NVivo 8.0 (QSR International, Southport, UK) to manage text and coding. Data analysis was undertaken as the interviews progressed, ensuring that emergent themes were analysed as they arose.

Transcripts of interviews were analysed in five steps: (i) identification of themes; (ii) generation of codes to label passages; (iii) revision of themes and coding scheme in light of newly accumulated data; (iv) application of codes to the final dataset; and (iv) exploration of the relationship of various themes amongst patients.

Interview transcripts were independently analysed and initial coding schemes generated by TFB and ARC; any variations in coding were resolved by discussion to achieve consensus. A third researcher, REF, also analysed the emerging coding framework to ensure rigour in the analysis. TFB elaborated the final coding scheme, and consistency was confirmed through blind dual coding with ARC. After 12 interviews, analysis showed that we had reached theoretical saturation, defined as the point when no new concepts or relevant data regarding a category emerge.[6]

Results

Fourteen adult survivors were interviewed, of whom eight (57%) were women, and age range was 21–82 years (mean 57 years). Data were classified into six main themes: survivors' understanding of SJS and TEN; their interpretation of why the ADR occurred; their experiences of the condition; the impact that the ADR has had on their current life, including their views towards the safety of medicines; views on medicines information sources; and their current views on events leading to the reaction with 'hindsight'.

A number of subthemes were also identified, and the resultant taxonomy is outlined in figure 1.

Circumstances Leading to Adverse Drug Reaction (ADR)

A variety of circumstances led to survivors developing SJS and TEN resulting in hospital admission. The most common causative drugs were antibacterials (nine cases), including penicillins, trimethoprim and cephalosporins; three cases were attributable to antiepileptics (phenytoin and lamotrigine), and the remaining two cases were attributable to allopurinol and sulfasalazine. The majority of events occurred in the community, with a few cases occurring in a secondary-care setting after the patient had been admitted with another complaint.

Understanding of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Survivors had a good knowledge and understanding of the condition. All were aware that their condition was drug-related and all but one knew the specific drug implicated. Most (11/14) survivors knew that the ADR was very rare; they recall either being told this directly by healthcare professionals caring for them at the time of the event or deducing this from the fact that they were treated as a 'novelty' while in hospital.

Most were also aware that it was potentially fatal (13/14) and that treatments were limited and largely conservative. Survivors and their relatives, however, expressed surprise at the seriousness of the reaction. Before the ADR occurred, they were

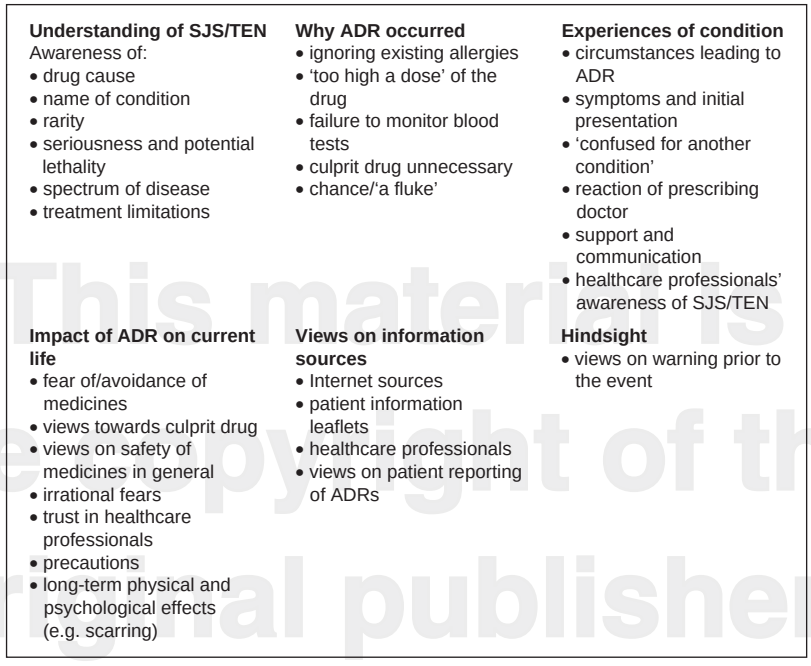

Fig. 1. Themes and subthemes identified through interviews with survivors. **ADR** = adverse drug reaction; **SJS** = Stevens-Johnson syndrome; **TEN** = Toxic Epidermal Necrolysis.

not aware that such serious reactions could occur as a result of taking medications; this is illustrated by the comments made by patient 7 below.

Patient 7 (21-year-old male): "I didn't know people could be ill like that. Being fourteen, I didn't know that … well fourteen to fifteen, I just didn't … (long pause)."

Interviewer: "You didn't think it could happen to someone like you?"

Patient 7: "Yeah, I'm just surprised in a way that allergies of that severity could happen."

Interpretation of Why the ADR Occurred

Survivors held different beliefs regarding the cause of the ADR. Only two survivors believed that the reaction was unavoidable and correctly understood that it could not have been predicted by healthcare professionals, putting it down to 'chance' given its rarity.

The majority, however, believed that the reaction was avoidable. Expressed views of its cause included being given too high a dose of the drug (three survivors), medical staff ignoring existing allergies (three survivors) and failure to monitor blood tests (one survivor). Those with existing allergies, for example, felt that this should have alerted the prescriber that they were 'at risk' and the culprit drug should therefore not have been given to them, as illustrated by the quote below:

Patient 4 (70-year-old female): "Well I felt bitter that I should not have been given cefalexin, but it was on my notes it said I'm allergic to penicillin … and there is a train of thought that cefalexin is closely related to penicillin, and she [the GP] shouldn't have given me that knowing my history, all my notes say no penicillin …. I feel she [the GP] should have looked it up on the Internet, she's got the means, she should have inquired rather than handing out willy-nilly …"

One survivor believed that the drug prescribed was 'unnecessary' for the condition he presented with and hence the reaction could have been avoided. Those who believed that the reaction was avoidable also expressed less trust in healthcare professionals.

Other quotes illustrating survivors' interpretations of why the ADR occurred can be seen below.

'A Fluke'

Patient 8 (82-year-old male): "… Allopurinol …, I mean, it's a standard gout cure I understand … but it went the wrong way … I mean I've no worry about the way the GP dealt with it, so it was a perfectly proper thing to do. It's just a fluke that it hits one in a million."

Ignoring Existing Allergies

Patient 6 (66-year-old female): "I have a history of allergy and I have had two very serious reactions, one when I was 29 and the other about 20 years ago and I had warned the hospital that I was allergic to penicillin and anything associated, but it's a bit of a factory there and everybody gets cephalosporin, I don't think anybody really questioned the fact that there was a relationship between cephalosporin and penicillin … I did make a point of saying to Dr D. I am allergic to penicillin when he came to do the pre-op visit. I don't think he took sufficient notice of that …"

Too High a Dose

Patient 12 (54-year-old male): "I reckon, it's a dreadful thing to say, I reckon my GP had taken his eye off the ball when it came to my blood tests, maybe the doses I was on was too much for me, maybe something a bit more modest would have been a bit more appropriate for me, I mean who knows …"

Patient 2 (44-year-old female): "But the epileptic nurse came by, she did say, ooh this seems a high dose for someone who's only had one fit! … my lips was really sore, they was like all gone black, it was like a crust, it was terrible… but um, perhaps if it had been a lower dose, perhaps it might not have happened."

Experiences of the Condition

Survivors vividly recalled how they first presented with SJS or TEN and the initial symptoms they experienced. The majority of survivors recalled experiencing 'lip swelling', 'blisters' or 'ulcers' affecting the skin and oral mucous membranes, with extensive 'shedding of their skin' and severe pain as a result:

Patient 2 (44-year-old female): "… and they started me on some epileptic tablets which were called lamotrigine … and the tenth day, all my eyes swelled and my lips … it was like blisters, constant diarrhoea really, and severe pain going to the toilet, and generally in a lot of pain, because it was like my skin coming off my body really."

Several expressed surprise at the perceived lack of awareness of SJS and TEN amongst healthcare professionals. Some patients recalled that their signs and symptoms were initially confused for other conditions, including chicken pox, oral thrush, *Herpes simplex* infections and viral upper respiratory tract infections, by both themselves and healthcare professionals:

Patient 1 (75-year-old female): "Well, I'd never heard of it, and when the doctors themselves didn't know anything about it, it was all a bit scary …"

Interviewer: "Do you find it surprising that some people [doctors] didn't know what it was?"

Patient 1: "I am surprised about it, because as I say, I'm not the only one and if they [the doctors] don't know, how do they get on?"

The majority of survivors (11/14) were seriously ill with the condition, and around half spent time in an intensive care unit after admission to hospital.

Support and Communication During the Event

Most patients felt well supported both by their GPs and, in particular, by the healthcare staff caring for them during their admission. They recall positive experiences of the medical and nursing care they received and felt that they were given adequate information about the condition, treatment and prognosis.

Survivors who were managed in specialist dermatology centres or burns units felt better supported and managed than those who were not. Those initially managed in non-specialist centres describe feeling under-supported, primarily, they believe, because the hospital lacked the facilities and experience to care for them.

The husband of one survivor, initially managed in a non-specialist centre, contacted the manufacturer of the implicated drug directly for more information as he felt he lacked information at the time of the event. Another survivor said that that the healthcare professionals caring for her could have communicated better, and that she was not allowed to be involved sufficiently in decisions regarding her care. She also felt that the staff were 'overwhelmed' by the severity of her condition and that although they could do little to treat it, they were not honest and open with her about this. These perceptions have damaged the trust and confidence that she now has in the healthcare system many years later:

Patient 14 (48-year-old female): "I did not have any answers whatsoever. Nobody would give me an answer. 'Oh I'll get back to you on that one.' And I didn't have any answers, and yeah, thinking about now, after I'd got through, they didn't know, and they didn't want to admit to not knowing, but I would have had more faith in them if they would admit it … I was asking 101 questions, it would have been nice for them to say 'look, I don't know', but they wouldn't."

Regardless of where they were managed, the majority of survivors and their families relied heavily on Internet sources for more information at the time of the event, with a few contacting patient support groups set up for sufferers of SJS and TEN.

Impact of ADR on Current Life and Views towards Medicines

Fear of or Avoidance of Medicines

The majority of survivors were currently fearful of or avoided taking medicines altogether. Some also expressed a marked fear of becoming ill enough to necessitate their use, implying that they fear that taking any medicine may lead to a similar adverse event.

One survivor, for example, admitted that she will avoid going to see her general practitioner (GP) if she had an infection of any kind, to avoid being prescribed antibiotics.

Patient 1 (75-year-old female): "But the only thing now is, it's made me so scared of taking pills…. I won't go to the doctors if I can help it now … um, you know if you got infections or any thing like that, I won't go, and if I had to go, was forced to go, he gives me tablets, I ask him … I must be the worst person, the worst nightmare they've had! [smiles] … I ask him, then I ask the chemist [laughs], then I think, I'm not taking them! Just in case, you know? It's frightening …"

Another survivor who had developed TEN after taking lamotrigine for newly diagnosed epilepsy, refused to take any antiepileptics after the reaction for a number of years, as she was too frightened to do so, and suffered from at least two serious epileptic fits as a result. She described how her fear also extends to her children when they are ill and require medicines.

Patient 2 (44-year-old female): "… what I found that happened when I came out of hospital, if I had a headache or anything, I was too scared to take any tablets, with C**** [patient 2's son], when he was 3 or 4, if he had a temperature … any other time, I'd just have the Calpol®, but I keep reading the instructions over and over again [laughs] … the one particular night, he did have a sickness bug, I felt as though my legs were shaking because I just couldn't cope … I'd read a Calpol® label, not once but half a dozen times [laughs] … thinking, I hope I'm doing the right thing!"

A few survivors also expressed fears regarding medicated supplements such as 'cough sweets' and certain foods, as illustrated by the quotes below.

Patient 7 (21-year-old male): "… I stopped taking any medication unnecessarily, like paracetamol, penicillin, Nurofen®, and … Lockets® [medicated lozenges], because they're like medicated inside aren't they … and, so I stopped taking all that kind of stuff … and I get really bad migraines as well, that will actually make me throw up, but I still don't take Nurofen® … because of the chance …"

Patient 1 (75-year-old female): "I think it's just made me aware of everything really … um, if er, if new sweets have come on [to the market] or anything … from different foods, you think, knowing that it's stupid! But it does … you think about it!"

Interviewer: "So if you're taking or eating new foods, you worry about it?"

Patient 1: "That's right; it goes through your mind, and I think, God, you're so stupid thinking this, when it's a medicine that's caused it, why should the food cause it? It's just psychological really."

Views Towards Culprit Drug

Interestingly, survivors did not appear to have negative views regarding the safety of the culprit drug in general, despite having had a serious reaction to the drug themselves. They are aware that although taking the culprit drug is life-threatening for them, this is not necessarily the case for others, including family members. They believe that the reaction is specific to themselves and their individual circumstances.

Views on the Safety of Medicines in General

The majority of survivors indicated that their views on the safety of medicines in general have not changed since the reaction, despite a change in their own medication-taking behaviour. They are aware that all medicines are associated with benefits and harms, and these have to be taken into account when deciding to take medications, as shown in the quotes below.

Views on using or prescribing medicines only when they are necessary were also discussed by survivors, including avoiding the over-reliance on or over-use of medicines.

Patient 14 (48-year-old female): "They're good as long as you understand the side effects of it. As long as you consciously understand the side effects of them, and again it's down to the individual on whether you want to, I want to … I need to know the worse case scenario so I can make my decision, consciously, because I've got to live with it."

Patient 10 (74-year-old male): "I suppose it depends how many … if you're taking medicines all the time, but suppose sometimes you've got to take it haven't you? As I said at the beginning you do take that risk but if you're taking it for a reason … like at the time I needed that, so that's why I took it …."

Patient 4 (70-year-old female): "Well … in general they're a good thing if they are not abused because there are a lot of patients with illnesses who are kept alive thanks to the medication, they've got to be used with common sense not just dished out willy-nilly …"

Trust in Healthcare Professionals

For some, the experience of a life-threatening reaction to a drug prescribed by a healthcare professional has diminished their trust in healthcare professionals, and advice given to them regarding treatment. A number of survivors described having less trust or 'blind faith' in what they were told by healthcare professionals since the reaction; this was particularly true of those who believed the reaction could have been avoided if the healthcare professional prescribing the drug had acted differently.

Patient 1 (75-year-old female): "… the only thing I feel is, you're scared … well I am, of going to the doctors, and he tells me you've nothing to worry about, and all this and that, but I'm still nervous of taking anything … he gives me antibiotics and he says you 'should' be alright with it, you should, but I said to him, I can't depend on his 'you should', I've got to be certain, if I'm not sure, I just won't take them."

Patient 3 (65-year-old male): "… you see that the public have got a blind faith in the medical world and I'm not so blind now, I'm more challenging …"

Patient 14 (48-year-old female): "I'm reading and since that happened and any medication I take, I'm reading everything before I'm taking it. Whereas previously, previously I was of the school of thought I use to think 'oh the doctor knows what he's talking about'. Now I'm going, 'they ain't got a clue, they can't be …' and that's the impression it's left on me."

Physical and Psychological Sequelae

The main long-term physical complication was cutaneous scarring, affecting survivors both physically and psychologically. Survivors discussed how scarring after the event has, for example, made them less confident, and reminds them of their traumatic experience.

Interviewer: "You mention your skin will never be the same. Has that changed the way you have to behave or live your life?"

Patient 11 (65-year-old female): "Yes, apart from what I wear, I've got to sort of think, I can stand that … sleeves, I keep wearing. My legs are a mess; I don't want to wear …" [struggles to speak, becomes tearful].

One survivor also appeared to exhibit symptoms of post-traumatic stress disorder.

Interviewer: "Do you think it has affected your life psychologically at all?"

Patient 13 (41-year-old male): "Yes … being depressed, yes, because as I said I get flashbacks, your memory goes but you remember certain things like when I'm having a shower or taking my top off or look in the mirror it all comes back again."

Interviewer: "You remember the events again?"

Patient 13: "Yes because I'm scarred in my mind as well as scarred on my body … I have flashbacks to my illness … the doctors were great and the hospital was great … but what let me down was the aftercare because ok, I got home and had to go back for check ups, but I said what about my scars? And the doctor was great he said you're a big strong lad, you'll be able to cope, but really I don't."

'Hindsight'

None of the survivors recalled being warned that SJS or TEN was a possible adverse effect prior to taking the drug. Survivors were rather philosophical, however, when asked whether they felt that they should have been warned, bearing in mind that the ADR was rare. They indicated awareness that many ADRs affect a minority of people. Interestingly, many stated that they would still have taken the implicated drug even if they had been warned, as all medicines are associated with a degree of risk.

Discussion

Survivors of drug-induced SJS and TEN generally had a good knowledge of the condition. There are only rare circumstances in which the risk of SJS and TEN can be determined prior to treatment; for example, the increased incidence of carbamazepine-induced SJS in individuals of Han Chinese ethnicity with the human leukocyte antigen *HLA–B*1502* genotype.[7] None, however, was relevant to our cohort. Nonetheless, patients formed their own and varied views of the cause of their ADR.

These beliefs have influenced their current views and attitudes towards medicines and their trust in healthcare professionals. Those who believed that the condition could have been avoided expressed more negative views on the safety of medicines and less trust in healthcare professionals.

The experience of a serious ADR had a profound impact on their current medication-taking behaviour, with many survivors avoiding medicines altogether or avoiding seeking medical attention when ill, regardless of the impact on their health. Some also had unsubstantiated fears, for example, of food supplements or medicated lozenges, possibly related to a lack of confidence in their ability to avoid a recurrence of the reaction.

Our study therefore highlights that clear communication with patients at the onset of life-threatening ADRs may be important, particularly those that could not have been reasonably predicted, such as SJS and TEN.

Patient education after the event may also be valuable. It would be important, for example, to explain to patients that those experiencing idiosyncratic ADRs such as SJS and TEN, are not more pre-disposed to experiencing other unrelated ADRs as far as we are aware; this might be helpful in reducing avoidance behaviour related to necessary medications in the future.

On the basis of this study, it is also apparent that after a serious ADR, patients' views on medicines and healthcare professionals were more positive if they perceived they had been given clear and honest information at the time of their illness.

Given the rarity of the ADR, it is unsurprising that many healthcare professionals were perceived by patients to know little about it, but interviews with survivors indicate that regardless of this, survivors preferred that healthcare professionals were open and honest about their limited

knowledge and the lack of definitive treatments available, and were keen to remain fully informed regarding progress in management and prognosis.

In our survey, survivors who were managed in specialist dermatology centres or burns units felt better supported and managed than those who were managed in non-specialist centres, implying that all patients with SJS and TEN should be managed in specialist centres where the expertise and facilities exist to deal with the condition.

These findings support existing objective evidence that early referral and management of SJS and TEN in a specialist unit leads to better outcomes, with reduced mortality and length of hospitalization.[8,9]

Based on our findings, we hypothesize that psychological support in the aftermath of a life-threatening ADR may be beneficial, and this should be explored. This might include support for sequelae such as loss of confidence due to scarring, and symptoms of post-traumatic stress disorder, which are not uncommon when an individual has experienced a life-threatening condition such as serious burn injuries, where skin loss and scarring sustained is similar to that seen in SJS and TEN, or after a critical illness requiring intensive care.[10,11]

Survivors and their families relied heavily on Internet resources, including online SJS and TEN support groups to obtain more information about the condition, and found these useful. Access to the Internet is increasing amongst the general population and, in particular, health concerns are the most common reasons for subscriptions to online services. Internet use, either directly or via friends or family, is widespread in patients experiencing cancer for example, with patients using the Internet to find second opinions and seek support and experiential information from other patients.[12] Social connections enabled by Internet support groups constitute a new forum of social support, that has largely unstudied potential.[13] The study of online support groups for those who have experienced ADRs such as SJS and TEN would therefore be a potential area for further research.

Finally, survivors are aware that many ADRs, including SJS and TEN, affect a very small minority of people, and believe that they still would have decided to take the drug even if they had been warned of the potential of developing the reaction. This supports the view that it may not always be necessary to warn patients of very rare ADRs, even if they are serious.

Limitations

Because of the rarity of the condition and its high mortality rate, it was not feasible to undertake formal purposive sampling, and hence our cohort may not be representative. Also, our findings cannot be generalized because of the qualitative approach used, although this is accepted as the aim of our study is to generate hypotheses and ideas, rather than test them.

In addition, the views of survivors of life-threatening ADRs such as SJS and TEN may differ from the views of those of other serious or potentially fatal ADRs. It may not be appropriate therefore to extrapolate out findings to patients who have experienced other serious ADRs.

Conclusions

Life-threatening ADRs such as SJS and TEN may continue to affect patients' lives long after the event. Patients' beliefs regarding the cause of the ADR differed, and may have influenced their trust in healthcare professionals and in medicines in general; clear communication during the acute phase of a serious ADR may therefore be important.

Our findings may be used as a framework for the understanding of other serious ADRs, and to improve the future management of patients with the condition.

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References

1. Pirmohamed M, James S, Meakin S, et al. Adverse drug reactions a cause for admission to hospital: prospective analysis of 18,820 patients. BMJ 2004; 329: 15-9
2. French LE. Toxic epidermal necrolysis and Stevens Johnson syndrome: our current understanding. Allergol Int 2006; 55: 9-16
3. Bastuji-Garin S, Rzany B, Stern RS, et al. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Arch Dermatol 1993; 129 (1): 92-6
4. Roujeau JC, Kelly JP, Naldi L, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. N Engl J Med 1995; 333 (24): 1600-7
5. Roujeau JC, Stern RS. Severe cutaneous adverse reactions to drugs. N Engl J Med 1994; 331: 1272-85
6. Strauss A, Corbin J. Basics of qualitative research. 2nd ed. London: Sage Publications, 1998
7. Chung WH, Hung SL, Hong HS, et al. Medical genetics: a marker for Stevens-Johnson syndrome. Nature 2004; 428: 486
8. Chave TA, Mortimer NJ, Sladden MJ, et al. Toxic epidermal necrolysis: current evidence, practical management, and future directions. Br J Dermatol 2005; 153: 241-5
9. Kelemen JJ, Cioffi WG, McManus WF, et al. Burn center care for patients with toxic epidermal necrolysis. J Am Coll Surg 1995; 80: 273-8
10. Patterson DR, Carrigan L, Questad KA, et al. Post-traumatic stress disorder in hospitalized patients with burns injuries. J Burn Care Rehabil 1990; 11 (3): 181-4
11. Cuthbertson BH, Hull A, Strachan M, et al. Post traumatic stress disorder after critical illness requiring general intensive care. Intensive Care Med 2004; 30(3): 450-5
12. Ziebland S, Chapple A, Dumelow C, et al. How the internet affects patients' experience of cancer: a qualitative study. BMJ 2004; 328: 564
13. Davison KP, Pennebaker JW, Dickerson SS. Who talks? The social psychology of illness support groups. Am Psychol 2000; 55 (2): 205-17

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