

# ANALYSIS

## Unhelpful information about adverse drug reactions

**Kirin Tan and colleagues** find that information about adverse drug reactions for commonly prescribed drugs is excessive, inconsistent, often poorly presented, and contaminated by symptoms commonly experienced in daily life. They suggest how we could do better

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Drug treatment is an important part of managing chronic disease, but people often choose not to start or continue with recommended treatments.<sup>1</sup> As the efficacy of a drug is central to the decision to start or continue treatment, accurate and succinct communication of the benefits of treatment is emphasised in clinical practice. But the disadvantages and adverse effects of drugs are also important. Concerns about adverse drug reactions—noxious and unintended effects of a drug (box 1)—can deter patients from starting treatment,<sup>2 3</sup> and their occurrence during treatment can prompt cessation.<sup>4 5</sup> Accurate information about adverse drug reactions, and its careful communication to patients, is likely to influence the outcomes of chronic disease management.<sup>6</sup>

An important concept in considering information about adverse drug reactions and its clinical impact is the nocebo effect, the phenomenon by which negative expectations promote adverse outcomes. Individuals who are aware they might get a certain side effect are more likely to experience it.<sup>6-8</sup> Participants receiving placebo in clinical trials report adverse events that strongly align with those of the active comparator treatment.<sup>9 10</sup> Experimental data indicate that informing participants of the possibility of a certain symptom increases reporting of it, compared with participants who were not informed of the possible symptom.<sup>11 12</sup> Administration of inert treatments leads to high rates of symptom reporting that aligns with the information provided before treatment.<sup>13</sup> Several symptoms, often referred to as “non-specific,” are commonly reported in nocebo research, including headache, musculoskeletal pain, difficulty concentrating, drowsiness, nausea, dizziness, fatigue, and insomnia.<sup>14</sup>

We extracted information from several sources about the number, type, and methods of presentation of adverse reactions for 15 commonly prescribed drugs—including metoprolol,

simvastatin, celecoxib, lisinopril, and quetiapine—and assessed the relation between adverse reactions listed for these drugs and commonly experienced symptoms. We investigated a range of “real world” sources of drug information accessed by practitioners and patients, so we included both official (a regulatory agency and a government funded source) and unofficial (two popular internet sites and a patient centred website) sources (box 2). We discuss the importance and implications of the content and presentation of information about adverse drug reactions for clinical practice.

### Finding information about adverse drug reactions

Information on prescription drugs is available from health practitioners, drug regulatory organisations, package inserts provided by the pharmaceutical company, compendiums of drug information, and internet based resources for professionals and the public run by various organisations. The information presented can come from a range of sources, including case reports, voluntary reporting by practitioners and patients, pharmacovigilance programmes, observational studies, and randomised controlled trials.<sup>15</sup> Most resources are online, and some provide information separately for practitioners and patients. Internet based resources are increasingly used by patients to access drug information: a survey in 2008 reported that 33% of Americans had searched the internet for drug information.<sup>16</sup>

### Too much information?

Figure 1 shows that the number of adverse reactions listed for each commonly prescribed drug is considerable: for eight of 15 drugs the median number is more than 50, and in no instance

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Extra material supplied by the author (see <http://www.bmj.com/content/349/bmj.g5019?tab=related#datasupp>)

**Appendix 1:** Adverse events for each drug from each information source

**Appendix 2:** Number and presentation of adverse drug reactions for 15 commonly prescribed drugs, according to information source

**Box 1: Terminology***Drug effects\**

*Side effect*—a secondary effect of a drug that might be adverse or beneficial

*Adverse effect*—an untoward occurrence in response to administration of a drug, which does not necessarily have a causal relation with the treatment

*Adverse drug reaction*—a response to a drug that is noxious and unintended and that occurs at doses normally used for prophylaxis, diagnosis, or treatment of disease or for modification of physiological function

*Seriousness*—a measure of the degree of harmfulness of an adverse response to a drug

*Severity*—a measure of the intensity of an adverse response to a drug

*Other<sup>6</sup>*

*Placebo*—beneficial effects produced by positive expectations

*Nocebo*—adverse effects produced by negative expectations

\*International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, [www.ich.org/](http://www.ich.org/)

**Box 2: Methods for analysis of information about adverse drug reactions***Drugs (indications) assessed*

- Alendronate (osteoporosis)
- Amlodipine (hypertension, ischaemic heart disease)
- Celecoxib (musculoskeletal pain)
- Clopidogrel (antiplatelet)
- Fluoxetine (depression)
- Frusemide (congestive heart failure)
- Metformin (diabetes)
- Lisinopril (hypertension, congestive heart failure)
- Omeprazole (peptic ulcer)
- Metoprolol (hypertension, ischaemic heart disease)
- Pioglitazone (diabetes)
- Quetiapine (psychosis)
- Simvastatin (hyperlipidaemia)
- Thyroxine (hypothyroidism)
- Levonorgestrel/ethinylloestradiol (contraception)

*Sources of information on adverse drug reactions*

- MedSafe (New Zealand Medicines and Medical Devices Safety Authority, [www.medsafe.govt.nz](http://www.medsafe.govt.nz))  
Separate information for consumers and health practitioners  
Separate information for branded and generic formulations  
Information from pharmaceutical company leaflets
- Drugs.com (a frequently accessed non-industry drug information website)  
Separate information for consumers and health practitioners  
Source of information not provided, even on request
- Yahoo Health (a commonly accessed health website, [www.yahoo.com](http://www.yahoo.com))  
No separate information for consumers and health practitioners  
Source of information not provided, even on request
- Patient.co.uk (a patient centred health website)  
No separate information for consumers and health practitioners  
Information from *British National Formulary* and pharmaceutical company leaflets
- National Library of Medicine (government funded information site, <http://druginfo.nlm.nih.gov>)  
No separate information for consumers and health practitioners  
Information from American Society of Health System Pharmacists

*Outcomes*

- Number and range of adverse drug reactions per drug
- Number and range of adverse drug reactions per information site
- Methods of presentation of adverse drug reactions
- Relation between commonly listed adverse drug reactions and commonly experienced symptoms

is it fewer than 26. Notably, the range of the number of adverse drug reactions listed for each drug is wide, such that at least one information source listed more than 40 adverse drug reactions for each drug except pioglitazone. More than 150 adverse drug reactions are listed by at least one source for each of fluoxetine, celecoxib, and quetiapine (see appendix 1).

**Too inconsistent?**

The number of listed adverse drug reactions varies markedly according to the source (fig 2). The median number of adverse drug reactions ranges from 15 to 70. The greatest numbers of adverse drug reactions are listed on the drug information website

www.drugs.com or in information for health practitioners on the regulatory authority website. In each case, the median number of adverse drug reactions listed exceeds 60. Two of the three sources with the lowest number of listed adverse drug reactions are the patient centred health website and the government funded drug information site.

Presentation of information about adverse drug reactions varies considerably across sources (see appendix 2). Although definitions of the frequency of adverse drug reactions exist (box 3), they are inconsistently applied. Two sources (www.yahoo.com and the National Library of Medicine) did not provide a numerical estimate of frequency of adverse reactions for any drug, and another two (MedSafe and www.drugs.com) failed to do so in the information designed for patients. One source (www.yahoo.com) provides information about frequency of adverse drug reactions, either numerical or descriptive, for only one of the 15 drugs. Some information sources emphasise frequency of adverse drug reactions using italic or bold type, underlining, or capital letters; other sources emphasise seriousness. There is inconsistency in information about seriousness of adverse drug reactions, which was provided for 13%-100% of individual drugs across the information sources. None of the information sources consistently indicates the type or level of evidence underpinning the adverse drug reactions listed. Disclaimers that some of the reported reactions might not be causally related to the drug were present for up to 20% of the drugs for all but one of the information sources (health professional information at www.drugs.com). In contrast, disclaimers that the list of adverse drug reactions might be incomplete are present for at least 40% of drugs at all sources except MedSafe documents for health practitioners and www.patient.co.uk.

## Overlap with common symptoms

In figure 3, the bar chart depicts the prevalence of the 20 symptoms most commonly reported in the previous seven days in a population based survey in which participants were recruited by random sampling.<sup>17</sup> Alongside each bar is the frequency with which the symptom is listed as an adverse reaction to the drugs we assessed.

Nine of the 20 symptoms most commonly experienced in daily life are listed as adverse drug reactions in more than half of drug information documents, and 17 are listed by more than a third (left column in fig 3). Eight of the 20 most commonly experienced symptoms are listed as an adverse reaction to more than 90% of the drugs by at least one information source (right column).

The substantial overlap between commonly experienced symptoms and frequently listed adverse drug reactions suggests misattribution of such symptoms as adverse reactions. This notion is supported by pharmacovigilance data that show that the adverse drug reactions most frequently reported by patients and practitioners are the symptoms most commonly reported in daily life,<sup>18</sup> and recognition that the non-specific symptoms commonly reported in nocebo research<sup>14 19</sup> align closely with those listed most frequently as adverse drug reactions. There is a lack of plausibility for a causal biological relation between the symptoms and many of the drugs assessed, a notable example being back pain and celecoxib.

## Potential for harm

Harm could result from excessive, inconsistent, and poorly presented information about adverse drug reactions. It might

deter patients from starting or continuing treatment. It could engender negative expectations in patients and health practitioners, which in turn will increase the frequency with which those adverse reactions are experienced and reported,<sup>6 14</sup> and the likelihood of treatment discontinuation. Inconsistencies about adverse drug reactions between sources in information can cause confusion among patients, which undermines their trust in health practitioners. This is a particular risk if a patient accesses an information source that lists large numbers of adverse drug reactions after a consultation with a health practitioner in which just a few adverse reactions were discussed.

Poor quality presentation of information can increase the nocebo effect. People have greater expectation of adverse reactions, expect more severe adverse reactions, and are less likely to comply with treatment if verbal or categorical descriptors of adverse drug reactions are used. Provision of numerical estimates of the risk of experiencing an adverse reaction reduces the nocebo effect.<sup>20</sup> Disclaimers that even more, as yet unreported, adverse drug reactions might occur in addition to those on the extensive existing list have the potential to exacerbate a nocebo effect. Finally, the current approaches to presenting information about adverse drug reactions could obscure the identification and quantification of the risk of serious or proved adverse reactions.

## A way forward

At present, organisations providing information about adverse drug reactions rarely document the levels of evidence that underpin it. When possible, information should be presented with the accepted hierarchy of evidence, including numerical absolute risk estimates, to allow patients to make informed decisions about treatments. Greater prominence should be afforded to data on adverse drug reactions available from randomised trials than from other study designs, as is the case in the assessment of drug efficacy. Common non-specific symptoms are often reported in clinical trials. For some drugs—such as  $\beta$  blockers, statins, and oral contraceptives containing oestrogen—existing data from placebo controlled randomised trials refute the associations with many of the non-specific commonly listed adverse reactions or allow the estimation and presentation of absolute risks of their occurrence.<sup>5 21-25</sup> Those adverse reactions, however, are still listed for each of those drugs by most information sources. Data on adverse effects of drugs that are now in routine use could be sought from existing data. Meta-analyses of existing randomised controlled trials of commonly prescribed drugs that examine their link with common non-specific symptoms should be undertaken and the results incorporated into drug information documents. An important caveat for use of randomised trial datasets in evaluating serious and/or uncommon adverse events is the inconsistent quality of reporting, influenced in part by academic and financial conflicts of interest.<sup>26 27</sup> Improved standardisation, collation, scrutiny, and analysis of adverse drug reactions will lead to more accurate and balanced information for patients and practitioners.

Observational studies have a clear role in the identification of rare and/or serious adverse drug reactions, those that occur during long term use that extends beyond the duration of exposure in randomised trials, and in assessing the incidence of adverse reactions in populations not included in clinical trials. Data generated in observational studies can have important biases that produce inaccurate estimates of causality or incidence, or both. For example, atypical femoral shaft fractures during long term use of anti-resorptive treatment for osteoporosis

**Box 3: European Union definitions of frequency of adverse drug reactions**

- Very common (>1/10)
- Common (1/100 to <1/10)
- Uncommon (1/1000 to <1/100)
- Rare (1/10 000 to <1/1000)
- Very rare (<1/10 000)
- Not known (cannot be estimated from available data)

first emerged from a case series<sup>28</sup> and are now accepted as causally related to treatment. In contrast, the concern raised by a pharmacovigilance programme that oral bisphosphonates might cause oesophageal cancer<sup>29</sup> was not supported by later studies and is unlikely to be valid. The limitations of observational studies can act in two directions. For rare but serious adverse drug reactions, observational studies tend to underestimate risk,<sup>30</sup> but for frequent less serious reactions, they can overestimate risk.<sup>18</sup> Particular caution should be exercised in attribution of causality of common non-specific symptoms to drug use from non-randomised studies to avoid inflating the volume and compromising the accuracy of information about drug adverse reactions.

Formats for concise and accurate presentation of treatment efficacy, such as the Drug Facts Box, have been reported to improve patients' understanding of drug treatments.<sup>31</sup> Incorporation of evidence based information about adverse drug reactions would complement such initiatives and improve the ability of patients to make informed decisions about treatments.

At a patient level, clinicians might use simple screening tools such as the perceived sensitivity to medicines scale,<sup>32</sup> a five item questionnaire that asks patients about their perceived sensitivity to the potential adverse effects of medicine and previous reactions to medicines, with their frequency and severity, to identify those at increased risk of nocebo responses and attempt to minimise such responses. For example, adverse drug reaction information provided to individuals at high risk of nocebo responses might reasonably be "contextualised" by considering the patient and disease being treated and the possible adverse effects of treatment.<sup>14</sup> This approach might minimise discussion of common non-specific symptoms and thereby nocebo effects, while maintaining patient autonomy.<sup>14</sup> While it might be construed as patronising not to discuss all commonly listed adverse drug reactions with a patient, it might also be counterproductive to do so because of the risk of inducing nocebo effects and non-adherence that could reduce the likelihood that effective treatments will be adhered to.

Emphasis of data from randomised trials, provision of numerical estimates of absolute risk of adverse reactions, discussion of the nocebo phenomenon, and positive framing of information about adverse drug reactions are strategies worthy of consideration in the attempt to improve outcomes from drug treatment of chronic diseases in individual patients.<sup>6</sup> In some circumstances when adverse reactions occur during drug treatment, consideration might be given to an n of 1 trial, which avoids the biases associated with unblinded rechallenge strategies, and can help individual patients in decisions about continuing treatment.<sup>33</sup>

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AG are endocrinologists with research interests in the translation of evidence to clinical practice. MJB helped to design the study and reviewed the draft manuscript. AG helped to design the study and analyse the data and wrote the draft manuscript. All authors reviewed and approved the final submission. AG is guarantor.

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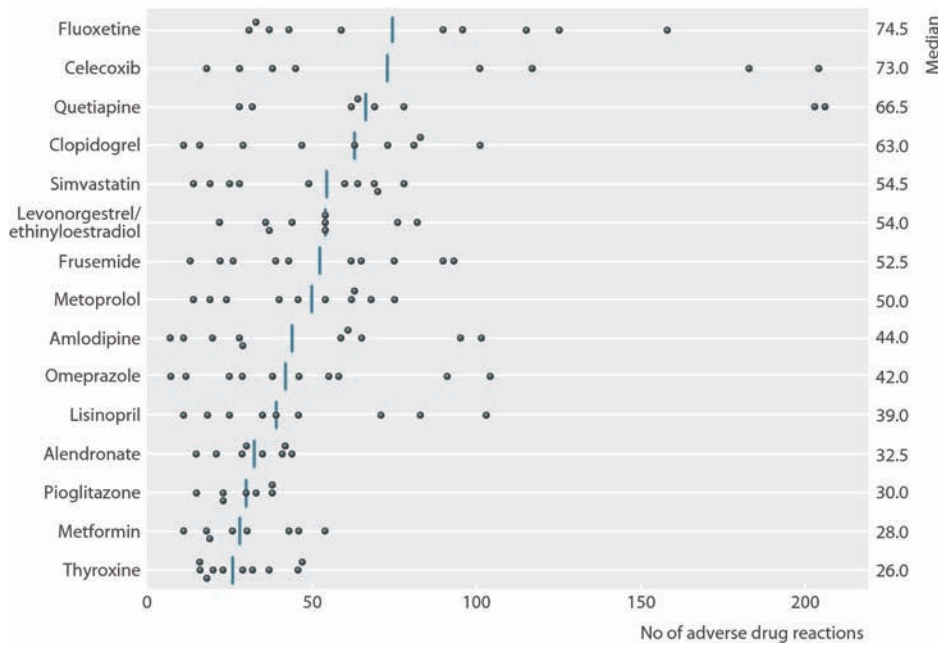
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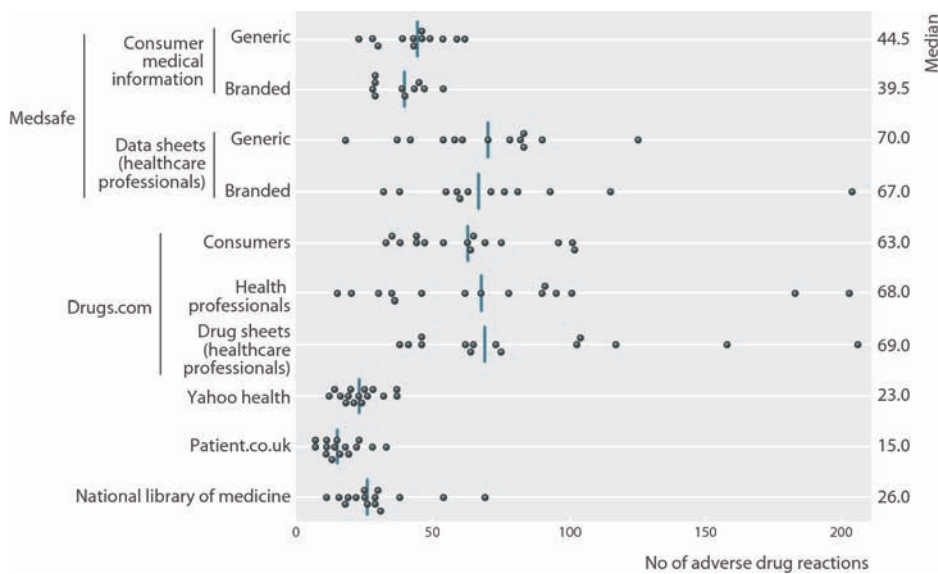
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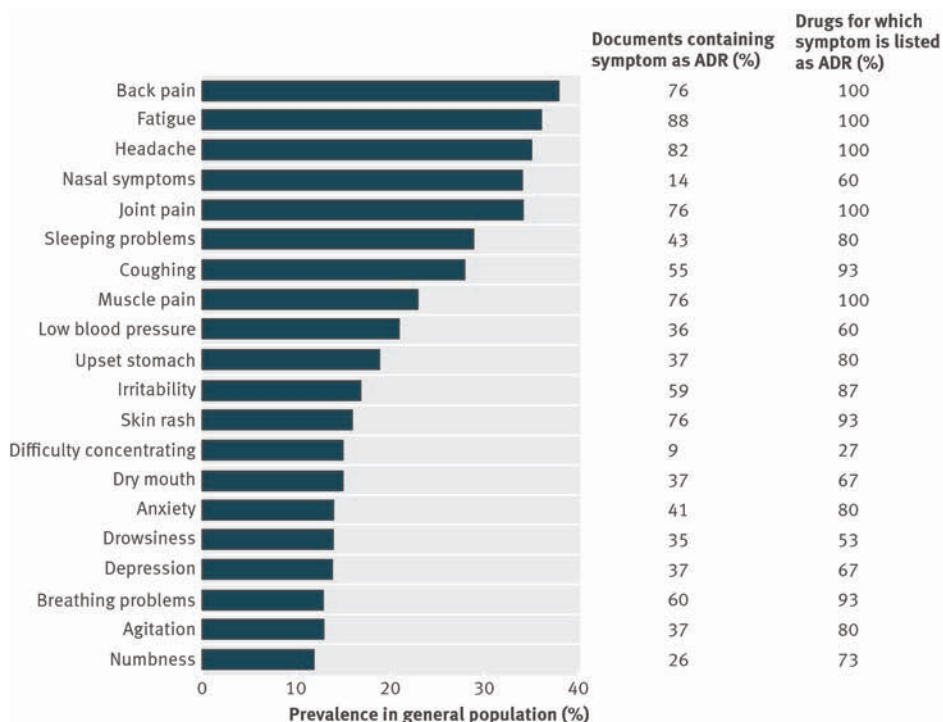
## Figures



**Fig 1** Numbers of listed adverse reactions for drugs commonly prescribed for chronic diseases. For each drug, each point represents one drug information document. Vertical bars are medians



**Fig 2** Numbers of listed adverse reactions for drugs commonly prescribed for chronic diseases at the indicated sources of drug information. For each information source, each point represents one drug. Vertical bars are medians



**Fig 3** Overlap between symptoms commonly experienced in daily life with those listed as adverse drug reactions. Bars indicate prevalence of indicated symptoms within the previous week in the general population. Also shown are proportions of drug information documents (n=136) in which indicated symptom is listed as an adverse drug reaction (ADR) and proportion of drugs (n=15) for which at least one source lists the indicated symptom as an adverse drug reaction