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Dyspepsia as an adverse effect of drugs

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Drugs are frequently implicated as a possible cause in new onset dyspeptic symptoms and few drugs are free of this suspicion. Nausea, anorexia, abdominal pain and dyspepsia make up between one-tenth and one-third of reported adverse reactions but they are all so common, both in the background population and among patients, that they are frequently attributed to an illness rather than to medications. No symptom or clinical sign is pathognomonic for adverse drug effects, maybe with the exception of vomiting. Dyspepsia is a common reporting in placebo-arms of treatment trials. Owing to the high background incidence of dyspepsia, it is difficult to discern between spontaneous and true drug-related dyspepsia. The mechanisms by which a drug causes dyspepsia are often unknown even though some drugs are known to cause direct mucosal injury. Non-steroidal anti-inflammatory drugs and antibiotics are common causes of drug-related dyspepsia.

Dyspepsia, defined as pain or discomfort centred in the upper part of the abdomen is a very common complaint, even among healthy individuals in the background population.

Dyspeptic symptoms are reported by 11% of healthy blood donors [1] and approximately 1.5% of the UK population consults a general practitioner (GP) for stomach problems each year.

Potential underlying causes include peptic ulcer disease, gastro-oesophageal reflux disease, functional dyspepsia and gastric cancer. Drugs are also frequently implicated as a possible cause in new onset dyspeptic symptoms and few drugs are free of the suspicion of causing abdominal complaints. Gastrointestinal (GI) symptoms such as nausea, anorexia, abdominal pain and dyspepsia make up between one-tenth and one-third of reported adverse reactions but they are all so common, both in the background population and among patients, that they are all too easily attributed to the illness rather

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than to the drug. Relationship to drug use is also obscured by variations in the terminology used to report GI symptoms. Dyspepsia is often defined as any symptom thought by the physician to originate from the GI tract, and may thus embrace a variety of symptoms such as nausea, early satiety, vomiting, epigastric pain, heartburn and even bloating. Others reserve the term dyspepsia for epigastric pain or discomfort [2]. Many reports of dyspepsia as an adverse effect of drug use do not define the term. At least in part as a consequence of this terminological confusion, epidemiological studies have produced differing estimates of the incidence and prevalence of dyspepsia, and of its association with potential risk factors, such as drug use (Table 1).

Estimating the relative frequency of dyspepsia as an adverse drug reaction is not easy. Dyspepsia is a common reporting in placebo-arms of treatment trials ranging from 2.3% to 4.2% in some studies [2]. On the top 20 adverse events list, by number of reports in the period 1969–2002, nausea is number four, vomiting is number nine and abdominal pain is number 13. The term *dyspepsia* is not on the list [3].

The newest version of the international encyclopaedia of adverse drug reactions *Meyler's Side Effects of Drugs*, published in 2006 [4] lists dyspepsia as a side effect to 46 drugs or drug classes. Additional information from the annual reportings from the same source from the years 2007–2008 adds another eight drugs to the list.

Keeping track with adverse drug reactions is a difficult task. In the period 1999–2003 6576 articles related to adverse drug reactions were published [4]. A search in PubMed using the MeSH headings '*dyspepsia*' and '*chemically induced*' produced 272 citations. 128 of these were published within the last 10 years and more than half (66/128) related to NSAID or aspirin use.

This review summarises current knowledge about dyspepsia, defined as epigastric pain or discomfort, as a side effect to drug use.

Methodological challenges in side effects research

The spontaneous reporting rate for adverse drug reactions that require hospital admission is in the order of 1% [5] and for less severe reactions the reporting rate is undoubtedly lower.

No symptom or clinical sign is pathognomonic for adverse drug effects, maybe with the exception of promptly occurring or persistent vomiting [6]. Even serious events, such as upper GI bleeding, may be missed for a long time as a possible drug-related effect, because the individual physician will see only few such cases. Interestingly, it took 39 years before the association between aspirin use and upper GI bleeding was recognised.

Incriminating a drug as a cause of a specific symptom, such as dyspepsia, requires use of the drug to be temporarily associated with the symptom, for the symptom to resolve when the drug is withdrawn and for it to reappear when a patient is re-challenged with the drug.

The temporal relationship between a drug and the side effect may not be very close, which is one reason why iatrogenic drug-induced disease – or symptoms – may be missed. Furthermore, patients are frequently on several drugs at the same time and the requirements to prove a causal relationship are thus seldom met. In everyday clinical practise the suspect drug is withdrawn but the subsequent challenge rarely pursued.

Table 1
Drugs that commonly cause dyspepsia.

NSAIDs
Cox2-inhibitors
Acetylsalicylic acid
Proton pump inhibitors
Bisphosphonates
Erythromycin
Tetracyclines
Sildenafil and tadalafil
Theophylline