

Pharmaceutical promotion and prevention of antibiotic resistance

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Introduction

The level of antibiotic resistance of typical human pathogens is correlated with community rates of antibiotic use.¹ For example, Southern European countries have both higher rates of antibiotic use than the Nordic countries and higher rates of bacterial resistance. A comparison between Spanish and Danish general practitioners found that Spanish GPs treated more patients with respiratory tract infections with antibiotics and used more broad-spectrum products.² Although in many Western countries, the volume of outpatient antibiotic use has remained stable or decreased, an international trend exists towards use of newer, more expensive broad-spectrum antibiotics.^{3 4} These should generally be considered second choice products, to be reserved for use after failure of narrower spectrum antibiotics or in patients intolerant to first-line drugs.

A Dutch study found that physicians who reported seeing pharmaceutical sales representatives prescribed higher volumes of second-choice antibiotics for respiratory infections.⁵ This is consistent with concentration of promotional spending on relatively new patented products.⁶ As is described in the examples below, promotion of newer antibiotics becomes problematic when companies' need to expand market share conflicts with public health objectives.

Z is for Zithromax

Pfizer's U.S. direct-to-consumer advertising campaign for azithromycin (Zithromax) stressed the product's convenience and need for fewer doses to treat children with acute otitis media (ear infections). The ads were inconsistent with U.S. Centers for Disease Control recommendations, which state that if an antibiotic is needed for acute otitis media, amoxicillin is the first choice. Azithromycin is costlier and no more effective, and is a broader spectrum antibiotic and therefore of greater concern in terms of development of antibiotic resistance.

Pfizer spent U.S. \$9.8 million on direct-to-consumer ads for Zithromax in 2000. By 2003, products sales were \$1.5 billion, making Zithromax the 5th most commonly prescribed medicine in the U.S.⁷ One of the most controversial aspects of this campaign was Pfizer's sponsorship of the pre-school television show, Sesame Street, accompanied by the statement that Pfizer was bringing parents "the letter Z as in Zithromax." Pfizer also donated a zebra, named Max, to the San Francisco zoo, and distributed thousands of plush zebra toys to U.S. physicians.

In 1999, Dr Sidney Wolfe, director of the U.S. consumer group Public Citizen Health Research Group, obtained an internal Pfizer memo that stated that an aim of the Zithromax promotional campaign was, "to counter CDC guidelines".⁷ Nineteen states subsequently sued Pfizer over the promotion of Zithromax. Pfizer was required to pay \$6 million, of which \$4 million covered legal costs and \$2 million the costs of public service announcements. These were to be broadcast over three cold and flu seasons and cost \$667,000 per year. The contrast between this amount

and the nearly \$10 million Pfizer spent advertising the product to the public in a single year – without counting promotional expenditures aimed at health professionals – is worth noting.

‘Max’ the zebra is not the only mascot used to promote antibiotics for paediatric use in the U.S. There is also ‘Auggie the froggie’ for Augmentin (amoxicillin/clavulanate) and ‘Bix the bulldog’ for Biaxin (clarithromycin). A marketing report credits the introduction of Bix the bulldog with a 39% increase in sales for Biaxin, from \$935 million to \$1.3 billion.⁸

Ketek (telithromycin): more beneficial or harmful than alternatives?

Aventis’ Italian advertisement for telithromycin (Ketek) shows an image of a white horse rushing through wild surf, with the headline, “*Ketek. The power of a new class in respiratory infections*” [translated]. In Taiwan, Aventis advertised Ketek as a first-line treatment for “everyday” respiratory infections. Both claims are inconsistent with the product’s characteristics. Telithromycin is a synthetic erythromycin derivative. Its mechanism of action, spectrum of antibiotic sensitivity and profile of resistance are similar to macrolides.⁹ Independent evaluators have contested the manufacturer’s claim that this antibiotic belongs to a new drug class.¹⁰ The suggestion that telithromycin should be used first-line for everyday respiratory infections raises concerns about the promotion of antibiotic treatment for viral infections and broadening of indications beyond approved uses.

In Canada, telithromycin is approved for community-acquired pneumonia, acute exacerbations of chronic bronchitis (AECB), and tonsillitis/pharyngitis, in patients intolerant to beta lactam antibiotics. In randomized controlled trials, it was found to be equivalent in effectiveness to amoxicillin (in community-acquired pneumonia) and clarithromycin (in community-acquired pneumonia and tonsillitis/pharyngitis), and was equivalent to cefuroxime and amoxicillin/clavulanate in AECB. A dose-related increase in QTc interval was noted at the pre-market stage, raising concerns about cardiac toxicity. Interactions with drugs with similar routes of metabolism, CYP 3A4 and 2D6, further lengthened the QTc duration in clinical trials. Telithromycin has only been compared with one macrolide, clarithromycin. Rates of diarrhoea, nausea and vomiting were higher with telithromycin than clarithromycin. Blurred vision, a rare adverse effect, occurred more frequently with telithromycin than comparators. In summary, the clinical trial evidence fails to support claims of superiority over existing alternatives, and raises concerns about safety.⁹

Sue wants to recover in time...

An Australian advertisement for Augmentin (amoxicillin/clavulanate) features a young, professional-looking woman, and the headline “Sue wants to recover in time to see her project launched”. A second headline asks physicians “For Sue’s sake” to take a closer look at resistance, and states that, “Augmentin delivers first time”. The implied suggestion is to use this drug first to avoid resistance, in contrast with a smaller-print boxed message stating the reimbursement criteria, which limit use to cases of suspected or proven amoxicillin resistance.¹¹

The appeal to physicians’ desire to please their patients, and patient perception of a quicker recovery with an antibiotic prescription, raises concerns about promotion of unnecessary antibiotic use for upper respiratory tract infections. The advertisement also provides conflicting messages in terms of promising that the product “delivers first time” and the need to restrict use

to cases of amoxicillin resistance. For the individual patient, the adverse event profile may also be a consideration, as higher rates of diarrhoea and elevated liver enzymes have been observed.¹¹

What do we know about the effects of drug promotion on prescribing?

There are many examples of advertising messages that promote widespread use of broad spectrum antibiotics. However, do these messages have any effect on prescribing practices?

Advertisements in medical journals are the visible ‘tip of the iceberg’ of a much larger promotional campaign. In 2002, the pharmaceutical industry spent \$21 billion promoting its products in the U.S., of which only \$480 million, or 2%, was on ads in medical journals.¹² These figures include the retail value of free samples although the cost to manufacturers is much less. However, even without including free samples, journal ads represent a small proportion of spending as compared with sales representatives, direct-to-consumer advertising, and sponsored scientific conferences and symposia.

Physicians tend to believe that promotion does not influence their own prescribing. For example, only 1% of 102 surveyed internal medicine residents believed that sales representatives had a lot of influence on their own prescribing; whereas 51% of the same respondents believed that sales representatives had a lot of influence on other physicians’ prescribing.¹³ Another U.S. survey found that physicians were less likely than patients to believe that gifts such as pens, mugs, or meals were influential.¹⁴ Physicians at one hospital who attended an all-expenses paid trip to a luxurious resort were asked whether they believed that attendance would influence their prescribing practices. On the whole, they did not believe that they would be influenced. However, prescribing data showed a strong influence.¹⁵ On a broader scale, an analysis of prescribing of five new macrolides in France from 1992 to 1998 found that shifts in prescribing rates for these products correlated closely with the volume of promotional spending and sales visits.¹⁶ A French independent drug bulletin had evaluated the contribution of these five products to therapy; none were found to offer therapeutic advantages over existing alternatives.

The availability of free samples can have a negative effect on prescribing. Boltri and colleagues compared first prescriptions for uncomplicated hypertension in a family medicine clinic during two time periods with and without samples. When samples were available, 62% of first prescriptions were of second-line drugs; when they were unavailable, 39% were for second-line drugs.¹⁷ Although this study examined anti-hypertensives, a similarity exists to antibiotics: in both cases first-line use of older, off-patent drugs is generally recommended.

A systematic review on the impact of physician-industry interactions was published in *JAMA* in 2000.¹⁸ The review included all studies published between 1994 and 1999 assessing the influence of pharmaceutical promotion on physician knowledge, attitude or behaviours. Most effects were negative. These included less ability to identify inaccurate claims, rapid adoption of new drugs, formulary requests for drugs without added value, increased prescribing volume and less cost-effective prescribing. One study found a negative effect on prescribing for uncomplicated illness but better knowledge of treatment protocols for complicated illness.

Little research exists on the content of pharmaceutical sales representatives’ presentations to physicians, but the available evidence suggests that inaccuracies favouring the advertised drug

are frequent.¹⁹ One survey by French physicians and pharmacists has operated continually since 1991. The results have been depressingly similar during the last 15 years: sales representatives rarely spontaneously mention adverse effects or contraindications, and in an important minority of visits (30-35%), they promote unapproved indications.²⁰

With the global withdrawal of rofecoxib (Vioxx) in September 2004, the potential for harm from drug promotion received extensive media attention. Rofecoxib was no more effective than existing drugs for arthritis pain and inflammation, but was largely promoted as safer. The first study to find a lower rate of complicated ulcers also found an increased risk of heart disease.²¹ Additional evidence of cardiac toxicity led to the product's withdrawal. In 2003, Merck spent nearly \$500 million promoting the drug to U.S. physicians and \$78 million to U.S. consumers. In an extrapolation based on clinical trial evidence and the rate of rofecoxib use, senior Food and Drug Administration official David Graham estimated that between 88,000 and 140,000 extra heart attacks occurred in the U.S., of which around 40% would have been fatal.²²

The World Health Organization (WHO-Europe) has described, “an inherent conflict of interest between the legitimate business goals of manufacturers and the social, medical and economic needs of providers and the public to select and use drugs in the most rational way.”²³ To get a new drug to market manufacturers do not need to provide evidence of therapeutic advantage over existing treatments. Drugs are generally tested against placebo. Antibiotics tested against comparators must be shown to be equivalent, not necessarily better. *La Revue Prescrire* in France evaluated the more than 3000 new drugs and indications approved in France from 1981 to 2004. They found only 0.2% to be major therapeutic advances, 2.5% important advances with some limitations, and 7.2% to be of some – but limited – value.²⁴ Even for ‘me-too’ drugs that are minor variations on existing chemicals and therefore cheaper to develop, investment costs must be recouped. This is as much the case, unfortunately, with antibiotics as with other drugs.

What is to be done?

We cannot continue to close our eyes to the effects of promotion on prescribing appropriateness and ultimately on public health. Drug promotion is one of a number of factors contributing to unnecessary antibiotic use, and inappropriate use of newer, broad-spectrum products, and therefore to antibiotic resistance. Regulation of promotion needs to be taken. This should include an evaluation of the types of regulatory strategies that do and do not work to ensure that promotional messages are consistent with public health aims, to prevent misleading messages from reaching health professionals and the public, and to correct existing misperceptions.

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