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Research paper

'You've got m@il: Fluoxetine coming soon!': Accessibility and quality of a prescription drug sold on the web

U. Gelatti[a,*], R. Pedrazzani[b], C. Marcantoni[c], S. Mascaretti[c], C. Repice[b], L. Filippucci[d], I. Zerbini[a], M. Dal Grande[e], G. Orizio[f], D. Feretti[a]

[a] Department of Medical and Surgical Specialties, Radiological Sciences and Public Health – University of Brescia, Viale Europa 11, 25123 Brescia, Italy
[b] Department of Mechanical and Industrial Engineering – University of Brescia, Via Branze 38, 25123 Brescia, Italy
[c] Post-graduate School of Public Health – University of Brescia, Viale Europa 11, 25123 Brescia, Italy
[d] Food and Health Research Centre for Altroconsumo, Milan, Italy
[e] Acque Veronesi S.c.a.r.l., Lungadige Galtarossa 8, 37133 Verona, Italy
[f] Department of Medical Prevention – Brescia Local Health Authority, Italy

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ABSTRACT

Background: The increasing phenomenon of online pharmacies has potential for serious public health problems. This study aimed to evaluate the possibility of accessing a prescription drug in the absence of a prescription for an Italian purchaser.
Methods: Fluoxetine pills were ordered from several online pharmacies. The study included website analysis, and the quality of the received product including packaging, chemical and microbiological analyses.
Results: Orders could be placed correctly on 61 of the 98 selected websites, and a sales transaction was concluded successfully on 17 websites. Thirteen drug samples were eventually received. In one case it was necessary to fill in a questionnaire before ordering the drugs. All websites displayed aggressive marketing strategies. There was wide variation in terms of domain registration, company base (when declared) and manufacturer's location (mostly India). All pills were delivered in sealed blister packs showing the lot number and manufacturer's details. A leaflet was enclosed in one case only. In three cases we received more pills than ordered, and in one case Viagra pills as a free gift. Pharmacopoeia microbiological requirements were satisfied. Chemical analysis revealed that the active principle was always present, although many samples did not meet the Pharmacopoeia "other impurities" or "total impurities" criteria. Heavy metals and solvents regulated by the Pharmacopoeia did not exceed the set limits; some of the non-regulated ones were also assessed, in some cases with a positive result (e.g. styrene).
Conclusion: About 20% of purchase attempts resulted in delivery of the drugs, even in the absence of a medical prescription. Traceability was poor and drug quality was generally worse compared to conventional pharmacy-purchased products. Based on all these broad-spectrum results, user safety appears not to be globally guaranteed.

Introduction

Internet applications have rapidly reached almost all fields of ordinary life, including the health service. Far from being merely a virtual place for information exchange, as conceived originally, the Web has become a means for accessing services and goods via "e-commerce" (Lowes, 2000). The sale of drugs has not been excluded from this revolution. Online pharmacies are companies which sell drugs ordered online and deliver the products by mail. First appearing in the late 1990s, they became so popular that the U.S. Food and Drug Administration (FDA) dedicated an entire website to them (Gallagher & Collaizi, 2000; FDA, 2010).

An announcement by the FDA highlights the "serious public health risk" associated with this phenomenon, since the sale of non-approved medicines and the illegal sale of approved ones are facilitated (FDA, 2007). Moreover, WHO has spoken out against the lack of quality control inherently connected with the system and pointed out the alarming percentage of counterfeiting (as high as 50%) among drugs sold online (WHO, 2009, 2010a, 2010b). The phenomenon is still very topical and has considerable implications in terms of public health. In a systematic review of web availability and purchases of medicines (Orizio, Merla, Schulz, & Gelatti, 2011) 47 of the 76 articles with original data published to January 2011 concerned samples from online pharmacies, and only 13 of them

* Corresponding author. Tel.: +39 0303717692; fax: +39 0303717688.
E-mail address: gelatti@med.unibs.it (U. Gelatti).

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involved in the online purchase of drugs. Moreover, the Web – especially online pharmacies – is characterised by extreme dynamism, thus information in such articles cannot be considered completely up-to-date – with only three articles published in the last three years (Bate & Hess, 2010; Dean, Klep, & Aquilina, 2010; Mainous, Everett, Post, Diaz, & Hueston, 2009). The European situation has been poorly investigated. One of the most complete studies, published in 2010 by Bate and Hess, analysed website features and assessed drugs in terms of price, purchase conditions and basic quality simply by checking the presence of the active principle (Bate & Hess, 2010).

The purpose of this study was to evaluate the actual possibility to access prescription-only drugs without a prescription, from the perspective of an ordinary European internet user in Italy. Unlike previous studies focusing on single or only a few aspects, the entire process was analysed, from the websites themselves to the quality of the samples received, which involved examining the packaging and conducting microbiological and chemical analyses, the latter to determine not only the effective presence of the active principle but also any potential contamination. An overall geographical assessment of the phenomenon was also performed. An economic analysis of the present study has been published elsewhere (Levaggi, Marcantoni, Filippucci, & Gelatti, 2012).

Methods

Drug choice

Fluoxetine, a serotoninergic antidepressant (Prozac® is the universally best known trade name), was chosen as target drug based on the following considerations. First of all, it belongs neither to the class of supplements nor to the so-called "life-style drugs" (e.g. Viagra®), which are particularly prone to counterfeiting (EAASM, 2008). The investigation could therefore focus on the specific portion of e-commerce represented by self-styled online pharmacies. Besides, being common, fluoxetine was not likely to be difficult to find on the Web. Moreover, it is a typical prescription drug, with specific indications and documented side effects including increased risk of suicide, risks associated with exposure in pregnancy, and withdrawal (Kieler et al., 2012; Kobayashi, Ikeda, & Suzuki, 2011; Messiha, 1993; Perlis et al., 2007; Pupco, Bozzo, & Koren, 2011).

Website selection

Website selection was performed from December 2010 to January 2011 via the Italian Google search engine, by entering 15 key words/phrases: "prozac", "fluoxetine", "fluoxetina", "prozac *vendita*" (the Italian word for "sale"), "fluoxetina vendita", "prozac sale", "fluoxetine sale", "prozac selling", "fluoxetine selling", "buy prozac", "buy fluoxetine", "online pharmacies", "*farmacie* online" (Italian for pharmacies"), "drugs online" and "*compra farmaco*" (Italian for "buy drug"). The first 30 results for each key word/phrase were selected and the following exclusion criteria were applied: websites not available in English or Italian; websites not leading to the required content within three clicks of the occurrence (based on the finding that users tend not to browse beyond the first result pages (Spink, Wolfram, Jansen, & Saracevi, 2001); websites clearly clones of an already selected website (completely identical website); and websites not delivering in Italy.

Drug ordering

A prepaid credit card, an and a P.O. Box were arranged. The bare minimum order for performing chemical and microbiological analyses (estimated as 80 20-mg tablets) was placed for each drug sample. Orders were placed for the generic formulation, as it is cheaper, so probably more tempting for a common user. In a few cases a brand product (Prozac®) was also ordered for comparison with generic products. When requested, a questionnaire on the purchaser's state of health was filled in using a standard profile, excluding any possible contraindications in order to maximize the probability of receiving the drug samples.

Website analysis

When the purchase orders were successfully concluded (i.e. financial transaction completed), the websites were analysed using content analysis (Riffle, Lacy, & Fico, 2005), evaluating formal and substantial topics via a codebook. Formal topics comprised name, extension, available languages, company accessibility, geographical position and domain (macro-areas) registration, the latter information being obtained from relevant websites: *whois.net* and *whois.domaintools.com*. Substantial topics concerned presence of marketing strategies, presence of highlights regarding the drug's possible adverse effects and request for a medical prescription. More specifically, we investigated whether the compilation of a questionnaire was required and whether this was expressly related to the issuance of a medical prescription. The presence of quality marks/certification was checked as well, such as the NABP (National Association of Boards of Pharmacies, a professional organization of U.S. pharmacies) lists of recommended and non-recommended online pharmacies (NABP, 2011a, 2011b), the Pharmacy Checker (an independent group indicating whether websites comply with the laws in the countries in which they are registered) (Pharmacy Checker, 2011) and the CIPA (Canadian International Pharmacy Association, a Canadian association of authorised online pharmacies) marks (CIPA, 2011).

Drug analysis

Each sample obtained underwent a three step analysis – packaging, microbiological and chemical – to assess whether the current regulations on pharmaceutical products were complied with and whether there might be risks to human health. A box of fluoxetine was purchased from a local pharmacy (pharmacy-bought product) to allow a more complete comparison in terms of quality and quantity. The packs were opened under laboratory hoods to avoid microbiological contamination.

Analysis of the packaging

After evaluating the pack conditions, we determined for each drug received whether the pills were loose, presented in a blister pack or in an inappropriate box. Product traceability was investigated by looking for the lot number and manufacturer's details on the original packaging. For a global check, the following aspects were considered: presence of a leaflet and the language used, presence of a medical history questionnaire and/or a medical prescription, number, dosage, macroscopic appearance of the pills, presence of advertising materials, and presence of additional free drugs.

Microbiological analysis

The microbiological quality of the pharmaceutical preparations was evaluated according to European Pharmacopoeia (EP) 5.0 for oral non-sterile products (EP 5.0 2004). Total viable aerobic count (bacteria and fungi: not more than 10^3 bacteria and not more than 10^2 fungi per gram of product) and absence of *Escherichia coli* were determined. The sample was prepared by dissolving 10 g of product in buffered sodium chloride-peptone (buffer peptone water 0.1% Tween) solution at pH 7 to obtain a 1:10 dilution. A different number of capsules was dissolved for each product due