

Over-the-counter and purchase-on-internet medications - Implications for psychiatry

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An unquestioning belief in the power and efficacy of nature's healing remedies and processes, the placebo effect, disappointment and dissatisfaction with conventional medicines, outright rejection of orthodox treatments, convincing and persuasive advertising, reinforcement from others with similar views, endorsement by influential celebrities, perceived hand-me-down wisdom, bogus pseudoscientific claims, uncritical journalism, scare-mongering, feelings of desperation for a 'cure', and anecdotal case studies or surveys masquerading as research, are among the many reasons why patients and the public choose to alternative medicines either bought through local stores, pharmacies or on the internet. Over-the-counter drugs (OTCs) or over-the internet remedies are taken either with or without conventional medicines by millions of people every year and while most are harmless and safe to use there are inherent dangers of additive effects and interference with prescribed medications.

Benefits for patients who use OTCs include the convenience and sometimes less costly outlay on prescription drugs (analgesics, for example). Preparations may vary in price, according to the pharmaceutical provider. Self-treatment of minor ailments should theoretically lead to less pressure on GPs. Unfortunately, some patients tend to self-medicate for long periods (for example, analgesics) without visiting their GP for a health check to monitor the condition(s) for which they are using the OTC remedy to begin with. There is also the incorrect but widespread belief that because a prescription is not necessary to obtain these drugs they must be much less harmful than prescription-only preparations. Medicines may be used inappropriately, such as paracetamol for insomnia, or aspirin for stomach aches. Very often no record of OTCs is documented in the patient's notes. The list of OTCs is too numerous to cover in any detail here and for practical reasons the authors will concentrate on common legal products which most people are familiar with.

What causes the adverse effects?

An understanding of drug interactions gained momentum through the study of metabolizing enzymes. Cytochrome P450 inhibition or induction is probably the main mechanism for the pharmacokinetic interactions of drugs. CYP450 enzymes are haemoproteins (like haemoglobin) which comprise many

related though distinct enzymes referred to as CYP. Over 70 CYP gene families have been described so far and are further divided into families and subfamilies of which CYP1, CYP2 and CYP3, are involved in hepatic drug metabolism.¹ Thus, CYP3A denotes a cytochrome P450 enzyme that is a member of family 3 and subfamily A. It is abundant in liver and intestine. In the liver CYP450s are found mainly in the smooth endoplasmic reticulum. Any inhibition of CYP enzymes may result in enhanced plasma and tissue concentration of drugs, leading to toxicity. Likewise, induction may result in reduced drug concentration leading to decreased drug efficacy and treatment failure. Tricyclic antidepressants are substrates of 2D6 (CYP450 2D6 in full), which inactivates them by hydroxylation. For example, if a tricyclic antidepressant is given concomitantly with the serotonin/ noradrenaline reuptake inhibitor venlafaxine, the levels of the tricyclic antidepressant will rise because venlafaxine inhibits CYP450 2D6 and therefore prevents the breakdown of the tricyclic compound. Similar effects can occur with paroxetine, duloxetine, fluoxetine and atomoxetine. However, in clinical practice only atomoxetine requires dosage reduction when given with a 2D6 inhibitor.²

Diphenhydramine (a common ingredient in sleeping tablets) in therapeutic doses inhibits CYP450 2D6-mediated metabolism of venlafaxine in humans. Venlafaxine has a low potential to inhibit the metabolism of substrates for CYP2D6 such as imipramine and desipramine compared with several of the most widely used SSRIs, as well as the metabolism of substrates for several of the other major human hepatic P450s.³ Of all the marketed drugs, about 60% are metabolized by the CYP450 system. The presence of the latter in red blood cells and hepatocytes contributes to the first-pass metabolism of drugs. This will have add-on effects when CYP450 inhibitors are simultaneously ingested. For example, grapefruit juice inhibits this enzyme system and therefore the bioavailability of drugs taken by mouth will increase causing a reduction in first-pass effect (presystemic metabolism).⁴

Common varieties of OTCs

Many commonly used OTC preparations (other than food supplements and analgesics) contain the ingredient dextromethorphan (related to codeine), used to treat coughs,

colds and flu symptoms. Up to 125 different types of cold medicines contain dextromethorphan. It is an effective cough suppressant (antitussive) that works by raising the coughing threshold. It is not an analgesic. Cough syrups and tablet or capsule forms of medicine that contain dextromethorphan may lead to loss of coordination, dizziness and, nausea when used in high doses. Dextromethorphan is the d-isomer of the codeine analogue of levorphanol which mimics morphine. It is relatively nontoxic and its antitussive effects last for about 6 hours. It should be avoided when an MAO inhibitor is concomitantly given.

The generic term antihistamine refers in general to the H₁ receptor antagonists used for inflammatory and allergic conditions. Sedation is a prominent feature of the H₁ antagonist, diphenhydramine, used for allergies such as hay fever (short-term beneficial effect) and for symptomatic relief of the common cold. Guafenesin, derived from the guaic tree, is a common ingredient found in cough expectorants. It is usually harmless though may cause problems in patients with compromised renal function. The mechanism of action, if any, is not known, save that it 'reduces viscosity' of respiratory secretions.

OTCs believed to help weight loss, such as laxatives, diuretics and diet pills, are often purchased either for genuine health concerns or for misuse. All have serious and potentially fatal side effects if taken for a long time, particularly electrolyte disturbances.⁵ Where diet pills are concerned problems may emerge insidiously with a few pills, quickly escalating to addiction. The alkaloid ephedrine is the principal active ingredient in the herb ephedra or ma huang. It is a potentially dangerous stimulant (sympathomimetic amine) contained in diet pills. Among the many possible side effects of diet pills are of course excessive weight loss with its attendant problems, alopecia, insomnia, and anxiety.

Used daily by millions of people worldwide, coffee and tea contain the methylxanthines caffeine and theophylline which act mainly by antagonism at purine receptors and by inhibiting phosphodiesterase. The effect is akin to a beta-adrenoreceptor agonist action. Caffeine is naturally found in certain leaves, beans, and fruits of over 60 plants worldwide. Its bitterness acts as a deterrent to pests. It can also be produced synthetically. Other than coffee and tea, the most common sources in the diet are cocoa beans, cola, and energy drinks. Product labels are required to list caffeine in the ingredients. Caffeine consumption in excess of 250mg daily produces symptoms indistinguishable from anxiety, including nervousness, irritability, tremulousness, muscle twitching, sleep disturbance, tachycardia, tachypnoea, palpitations, ectopic beats, and diuresis. A withdrawal syndrome can also occur and is associated with headache and a general muzziness. Caffeine may interfere with the effectiveness of drug treatment. For example, clozapine plasma levels can be raised, presumably through competitive inhibition of CYP1A2.⁶ In general terms,

an average cup of brewed coffee contains 100mg caffeine per cup, Red Bull 80 mg/ 250ml per can, tea 45mg/ cup, instant coffee 60mg/ cup and filter coffee 120mg of caffeine per cup. Excess consumption of Red Bull may cause myopathy due to caffeine-mediated hypokalemia and rhabdomyolysis.⁷

Paracetamol (acetaminophen in the USA) is metabolized in the liver. It is probably the most common household analgesic and is present in a variety of preparations and is usually well tolerated. Drugs that increase the action of liver enzymes which metabolize it for example, carbamazepine, isoniazid, and rifampin, reduce the levels of paracetamol and decrease its action. Doses greater than recommended may result in liver damage and in overdose a potentially fatal hepatic necrosis can occur.

Not much is known about the contents of home medication cabinets (HMCs), the management of leftover medications, and the inclination of patients toward self-initiated treatment using non-prescription drugs. One cross-sectional study conducted in 72 Belgian community pharmacies revealed that the most frequently encountered categories of registered medicines were NAIDs, nasal decongestants, and drugs used for nausea. Despite their high prevalence, NSAIDs and non-opioid analgesics did not predominate (14%) among the most frequently used drugs: food supplements were used daily in 23.3% of households. Twenty-one per cent of the drugs were expired, 9% were not stored in the original container, and the package insert was missing for 18%. Self-medication, although generally acceptable in terms of indication and dosage, was commonly practiced, also with prescription drugs. Taking into account that younger people showed a significantly higher rate of self-medication, awareness of the risks of self-medication is warranted.⁸

Relevance to Psychiatrists

Many psychiatric conditions are associated with excess alcohol use which complicates the picture when OTCs are used concurrently. Mixing alcohol with medication has the potential to cause nausea and vomiting, headaches, drowsiness, fainting, and loss of coordination. Because so many drugs can be bought without a prescription potential interactions with alcohol are often forgotten. Teenagers see OTCs as safer than illegal drugs and OTCs are sometimes taken to get a buzz or to help stay awake while studying. The home medicine cabinet allows quick access. Besides, parents will most likely have given an OTC preparation to their children for colds or other minor everyday ailments. Most drug education programmes however, focus primarily on illegal drugs, not OTC drugs and their potential for abuse.

Of some interest and importance to psychiatrists is the interaction when warfarin is combined with ginkgo (*Ginkgo biloba*) causing bleeding, a mild serotonin syndrome in patients who mix St John's wort (*Hypericum perforatum*) with serotonin-reuptake inhibitors. decreased bioavailability of

digoxin when combined with St John's wort, induction of mania in depressed patients who mix antidepressants and ginseng, exacerbation of extrapyramidal effects with neuroleptic drugs and betel nut (*Areca catechu*); increased risk of hypertension when tricyclic antidepressants are combined with yohimbine. Disulfiram which inhibits aldehyde dehydrogenase inhibits the metabolism of warfarin. Metronidazole causes an unpleasant disulfiram-like reaction when mixed with alcohol. Consumption of 6-8 glasses of grapefruit per day may raise levels of carbamazepine and pimozide. Grapefruit juice is thought to the metabolism of many drugs and inhibition can last a number of hours.⁹ The St John's wort component, hyperforin, contributes to the induction of CYP3A4. St John's wort also enhances the metabolism of other CYP3A4 substrates including the protease inhibitors indinavir and nevirapine, oral contraceptives, and tricyclic antidepressants such as amitriptyline. Other herbal remedies with the potential to modulate cytochrome P450 activity include ginseng, garlic preparations, and liquorice.¹⁰ Intake of St John's wort increases the expression of intestinal P-glycoprotein and the expression of CYP3A4 in the liver and intestine. The combined up-regulation in intestinal P-glycoprotein and hepatic and intestinal CYP3A4 impairs the absorption and stimulates the metabolism of cyclosporine, leading to subtherapeutic plasma levels.

The hormone melatonin plays a role in regulating the sleep-wake cycle but does not induce sleep *per se*. It is easily available through the internet and over-the-counter in the USA and many people use it for jet lag. Melatonin has side effects including diarrhoea, abdominal pain, headaches, nightmares, morning hangover, nausea, mild depression and loss of libido. Melatonin is used for many other complaints including tinnitus, depression, chronic fatigue syndrome (CFS), fibromyalgia, migraine and other headaches. Valerian root, a medicinal herb has been known to cause liver damage and should be used with caution. It too is most commonly used for insomnia and frequently combined with hops, lemon balm, or other herbs.

Many complementary medicines prescribed for anxiolysis/sedation (e.g. kava kava, valerian, passion flower and chamomile) are GABAergic, GABA (formed from glutamate) being the major inhibitory mediator in the brain, though for some, such as hops, the mechanism of action remains unknown. As expected, all remedies can lead to drowsiness when taken in high doses and can potentiate the effect of synthetic sedatives.¹¹ Kava has been taken off the market because of its hepatotoxicity.

Although sufficient dietary fibre and water are effective for the treatment of constipation some patients fear they are building up 'toxins' if they do not have 'regular' bowel habits. Often constipation is caused by opiate analgesics which are widely available, and in many cases patients are using antidepressant/psychotropic medication concurrently. The tendency to misuse laxatives is commonly seen in anorexia

nervosa though is not confined to that disorder. The osmotic laxative lactulose is a disaccharide of galactose and fructose and therefore care is needed where diabetic patients are concerned particularly if they are taking neuroleptic medications such as clozapine or olanzapine. Abdominal cramps and diarrhoea can occur with high doses. Laxatives have the potential to interfere with potassium levels, usually causing hypokalaemia.⁵

Ordinary foods and drinks may interfere with prescribed medications.¹² Grapefruit juice reduces the metabolism of calcium channel antagonists. Vegetables such as broccoli, cabbage, and Brussels sprouts are putative cytochrome P450 inducers and are known sources of vitamin K. Red wine, ethanol and cigarette smoke are also believed to induce the cytochrome P450 system and have the potential to interfere with the metabolism and catabolism of many drugs. Smoking interferes with clozapine metabolism. When smokers are prescribed clozapine abrupt smoking cessation may lead to high plasma concentrations with potentially serious consequences. Clozapine plasma concentrations can rise 1.5 times in the 2–4 weeks following smoking cessation,¹³ and in some instances by 50–70% within 2–4 days. Where baseline plasma concentrations are higher, particularly over 1 mg/litre, the plasma concentration may rise dramatically owing to non-linear kinetics. If patients smoking more than 7–12 cigarettes per day while taking clozapine decide to quit, the dose may need to be reduced by 50%.¹⁴ Smoking also interferes with duloxetine levels due to an induction of CYP1A2 by hydrocarbons contained in tobacco smoke. It cannot be expected that patients would be aware of these facts, let alone understand the pharmacology of the multitude of chemicals contained in OTCs.¹⁵

Availability does not mean harmless

Most people using OTCs are unaware of the potential for harm. Herbal remedies, for instance, with their attractive packaging, convey the impression of being beneficial merely because they contain 'earth minerals' and other 'natural ingredients': therefore they must be beneficial for health, rather like eating vegetables or taking vitamins.¹⁰ There are numerous instances of drug interactions and many preparations may contain contaminants such as mercury, lead, and arsenic. One of the commonest ingredients in many lotions and potions is hydrocortisone, which if used liberally may cause skin atrophy. The most worrying aspect of OTCs is that they give hope to people with serious conditions which might be better treated with conventional medicines - multivitamins for cancer, mineral supplements for constipation, and so forth. With buzz words such as 'healing, energy, vitality, harmony, body balance, healthy living, total well-being, holistic', and 'traditional', targeting the sometimes gullible consumer, OTCs become very appealing. Others are taken in by the pseudoscientific jargon, 'healing powers, purifying the blood, eliminating toxins from the bowel', boosting one's immune system, and so forth. The outcome can be serious: for example, Chinese herbal medicines

containing extracts from *Aristolochia* plants have been implicated in the high incidence of urinary tract cancer in Taiwan, a study has suggested¹⁶ because aristolochic acid has a consistent pattern of inducing DNA damage.

Some patients may be coincidentally taking conventional, proven medicines yet attribute their improved health to the alternative remedy. Other beneficial factors which are often conveniently ignored include a change in diet, increased wellbeing through physical exercise, or going on holiday! There is of course, the natural remission of the illness, particularly with transient viral infections, or unexplained lower back pain, to cite two instances.¹⁷

Some common problems

Although the dangers of the common analgesics are relatively well-known (paracetamol causing liver damage, gastrointestinal upset with ibuprofen), patients are often unaware of the potential for adverse effects with other preparations. Nor are they always aware that many compounds combine two analgesics, for example, paracetamol and aspirin, or paracetamol and ibuprofen. Nonsteroidal anti-inflammatory drugs (NSAIDs) interfere with renal clearance and may result in elevated lithium levels with resultant toxicity.¹⁸ Combined use of an antidepressant or sodium valproate with an OTC could lead to abnormal liver function tests attributed solely to the former agents and not the OTC. Even reading the label does not guarantee insight and understanding of what is on offer. Labels are carefully and handsomely packaged by advertisers to persuade people their product is better than conventional medicines. Most consumers spend little time reading the labels about ordinary foodstuffs, never mind the chemical constituents of OTCs. In transplant patients, self-medication with St John's wort (*hypericum perforatum*) may lead to a drop in plasma levels of the immunosuppressant drug cyclosporine, causing tissue rejection. In the US, the Food and Drug Administration (FDA) with branches in other cities, including London (European Medicines Agency) approved a regulation in 1999 requiring that all OTC drug labels contain certain information such as ingredients, doses and warnings in a standardized format. This covers thousands of non-prescription products, including sunscreens. In the same way that people understand the nutritional value of foods, it is hoped that its efforts will help people use OTCs safely.

Sexual side effects are a frequent accompaniment of psychotropic drugs and patients are often bothered by impotence to such a degree they resort to surfing the internet to acquire sildenafil (Viagra) and the like. Such over-the-internet medicines are easy to acquire. Carbamazepine and St John's will decrease the level of sildenafil by competition with CYP3A4. Ketoconazole, the antifungal agent, works in a similar mechanism and may increase the levels of citalopram. Metronidazole has a disulfiram-like reaction with alcohol.

There is also the problem of addiction with OTCs because of ease of access to opioid compounds. Patients often do not perceive them as having addictive potential. Preparations containing ephedrine or dextromethorphan can be abused. Ephedrine is still used as a nasal decongestant. As an indirectly-acting sympathomimetic amine it can react dangerously with monoamine oxidase inhibitors because of the increased amount of noradrenaline stored in noradrenergic neurones. Opioids may be crushed and the powder snorted or injected leading to euphoria or elation, followed by addiction when compulsive use takes over. Patients may be subject to mood swings making underlying psychiatric disorders and drug treatment difficult to manage. Opioids produce drowsiness, and depress respiration in high doses. The combination with sedative psychotropic medication such as mirtazapine, olanzapine or quetiapine could be deleterious especially where there is concomitant weight gain. Buspirone (a 5-HT_{1A} receptor agonist used for anxiety) may interact with monoamine oxidase inhibitors (MAOIs), such as isocarboxazid, phenelzine, and tranylcypromine. Use of buspirone with these drugs can increase blood pressure. The combination of buspirone and trazodone may raise LFTs. The combination of buspirone and warfarin may accentuate the effects of warfarin and increase the risk of bleeding. Patients taking buspirone should not drink grapefruit juice, since even some time after a dose is taken, the amount of buspirone in the blood may be increased. Carbamazepine increases the metabolism of the pill reducing its effectiveness. The pill is more easy to acquire now (clinics and/or the Internet) and therefore unexpected pregnancies may occur in patients taking both. Cimetidine may increase the blood levels of sertraline by reducing its elimination by the liver. St John's wort interacts with the metabolism of the pill and this can result in unwanted pregnancies.

Overall OTCs are generally safe, though not where young children and pregnant women are concerned. Vitamins are safe unless taken in very high doses. Deficiency is rare in developed countries (apart from vitamin D) and therefore they are often taken unnecessarily 'to achieve balance' or for 'vitality and energy', and other eye-catching spurious claims. Glucosamine, an amino sugar, seems to be the most popular OTC dietary supplement for the treatment of osteoarthritis. It is naturally present in shellfish and in some fungi. Apart from occasional allergic reactions and mild gastrointestinal symptoms, it is generally innocuous, though conclusive evidence for its efficacy in osteoarthritis is lacking. Fish oil supplements usually come from mackerel, herring, tuna, halibut, salmon and cod. There is some evidence that omega-3-fatty acids contained in fish oils are beneficial for cardiovascular problems but more trials are needed. Side effects are minimal and include mild gastrointestinal upset.¹⁹

Doctors' dilemma

Is there a solution? Probably not, though one way to increase consumers' awareness of the dangers associated with OTCs

could be to change their status to match that of drugs such as simvastatin—they would still be sold over the counter, but with a pharmacist's supervision. The list of OTCs is rising leading to increased intake of phytochemicals in addition to the usual gamut of medicines used to treat upper respiratory infections. Potentially fatal interactions can occur with OTCs and traditional drugs. Providing better training for pharmacy staff, and restriction of the quantity sold per customer, should also be considered, though with so many retail outfits selling these products this is probably unrealistic. Besides, many of these products are available on the shelves, not necessarily at the pharmacy counter.

The most common addictions are combinations of opioids with standard analgesics. The Internet is an easy source for prescription drugs, increasing their availability and eliminating the need to see a doctor. Is there an epidemic of prescription opiate use? It is difficult to tell. Effective prevention, public information, and treatment policies require sound epidemiological data about drug use to ensure policy-making is not distorted by stories of celebrity arrests and media-generated hysteria which tend to give that impression that use of illegal drugs is rife. The lack of knowledge about the ubiquitous presence of unknown ingredients in OTCs may be a source of concern in the future when even more become easily available.

It is difficult for doctors and other health care professionals to advise patients on the effectiveness and safety of OTCs. The numbers of well-designed studies available for review are limited, often conducted in a small number of healthy participants, and for short time periods only.²⁰ A survey conducted by questionnaire in 238 follow-up UK rheumatology outpatients in three centers found nearly half (44%) had taken various herbal remedies or over-the-counter (OTC) preparations over the past 6 months. The most commonly used were: cod-liver oil, glucosamine, and/or chondroitin, and evening-primrose oil. Rheumatology outpatients have a particularly high risk of interactions with conventional medication because of polypharmacy and comorbidity. Ginkgo biloba, devil's claw, ginger, and garlic may have antiplatelet or anticoagulant effects and may exacerbate the gastrointestinal bleeding risk of nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids. Echinacea (taken by 4%) may be hepatotoxic and could exacerbate the adverse effect of disease-modifying antirheumatic drugs (DMARDs). Most patients are unaware of the potentially harmful interactions.²¹

The authors carried out a small audit of consecutive outpatients and staff on a random basis seen in our unit. Of the 45 people who completed the questionnaire 70% affirmed use of OTCs, either presently or in the past. A high percentage (73%) had never been asked by their GP about these 'alternate medicines' and among health professionals 25% never enquired from patients about the use of OTCs. More than half (63%) were unaware of possible side effects before taking them and nearly 50% had not considered that the OTCs might interact with

prescribed medication. As would be expected, the majority of users (84%) did not experience any side effects. Nonetheless 16% experienced unpleasant adverse effects such as tachycardia, nightmares, drowsiness, cough, constipation, and exacerbation of asthma. When asked who had recommended the preparation/s the response was generally, 'friends' or 'I knew about it myself'. When asked why they bought it over-the-counter, the response was 'just in case I need it', 'cheaper than prescription' 'it is a natural remedy' 'it's only Nurofen'. As with most surveys, the commonest preparations were analgesics, laxatives, glucosamine for arthritis, and decongestants. Others bought OTCs to promote good health because they are herbal and natural', for example, ginkgo biloba. In a separate random survey of 50 consecutive outpatients carried out by FJD and N El-H, some 40% were taking herbal remedies.

Conclusion

Medical care has become fragmented in recent years. The family doctor of old no longer acts as a gatekeeper to coordinate medications patients are prescribed. A gynaecologist may prescribe the pill to a patient and a walk-in clinic may prescribe an antibiotic to the same patient. How does a doctor inform the patient that antibiotics decrease the effectiveness of the pill if the doctor is unaware of the myriad of other supplements including OTC medications, a patient is taking? Although a patient should bear some responsibility, in reality he/she may not have the expertise to discern the complications and interactions of medications. Besides multiple use of preparations is more often a problem of older age groups who frequently have many health problems. The family pharmacist has also been lost to mail-order pharmacies and sometimes suspect internet web sites. Because of the increase in numbers of prescriptions and OTCs, doctors and pharmacists are using computer programs to establish what is safe and what is not.

Strategies to mitigate these problems could include more general enquiries about prescriptions, OTC, and herbal drug use at the initial examination.²² Even though some patients may be aware of the potential for drug misuse, others are naive and do not realize the harm involved. Providing containers to enable patients to dispose of unused or unneeded prescriptions or OTC medications is another tactic. Treating the underlying causes (of pain, for example) more aggressively may obviate the need for patients adding OTCs to their drug list. Practicing careful record keeping of prescription refills and tightening controls over prescription blanks are other practical measures. Where patients have become addicted to medications, programmes such as Narcotics Anonymous may help.

None declared

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