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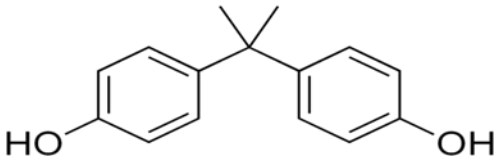
Health risks of Bisphenol-A contamination

Although Bisphenol-A (BP-A) is an endocrine disrupter, it is used in a large variety of consumer products including plastics, medical equipment, food linings and many other daily used items. BP-A leakage is enhanced by heat, acidic or basic pH as a result of ester bond breakage. Plastic toys are one of the main sources of BP-A exposure during childhood. Since Kuwait is one of the hottest countries in the world, we undertook a study to examine BP-A levels in four randomly chosen toys: plastic tiger, plastic Lego blocks, plastic doll and other small dolls, and in two different brands of drinking bottled water. These items were stored at 45^0C for 4 days and then Bisphenol A was extracted with 1 L of water and samples were analyzed by ultra-pressure liquid chromatography coupled with ultraviolet detector (UPLC-UV). This method has a limit of detection (LOD) of 0.4 ppb and a limit of quantification (LOQ) of 1 ppb.

Background

Bisphenols are carbon-based synthetic phenolic compounds containing two hydroxyphenyl groups. The chemical structure of these compounds is based on diphenylmethane, except for bisphenol S, P and M. Phenolic compounds are generally weak acids, however, they are considered relatively stable due to the existence of several mesomeric structures.

The reactivity of phenolic compounds mainly depends on the entire structure of the molecule and the nature of the substitutes attached to the benzene ring. The presence of hydrogen bonds affects their solubility in water, the boiling and melting point as well as the alteration of its infra-red (IR) and ultra violet (UV) spectra (Wilfred *and* Ralph, 2006).



Bisphenol A (BP-A) is a monomeric compound synthesized in the 1930s by Dodds and Lawson to mimic the estrogenic effect in humans. In the 1950s, BP-A was employed in making epoxy resins and polycarbonate plastics due to its desirable chemical and physical characteristics (Joe and Russ, 2011).

However, BP-A is a well-known endocrine disrupter. It is the building block for polyvinyl chloride, polystyrene, phthalates and polycarbonate plastics often used in various consumer products including medical equipment, tableware, plastic water bottles, toys, thermal receipts, pharmaceutical containers and food linings. Additional uses of BP-A include common household and workplace items such as the coating of CDs, DVDs, electrical and electronic equipment, automobiles and sports safety equipment (Beverly *et al.,* 2011). Plastics containing BP-A such as polycarbonate, polysulfone, polycrylates, polyetherimide and polyvinyl chloride are used in manufacturing intravenous fluid bags, respiratory masks, endotracheal tubes, umbilical catheters, nasogastric and enteral feeding tubes. Moreover, BP-A is involved in producing dental composite resins, dental sealants and other dental devices. Medical and dental materials have a direct and long contact with patients with slow BP-A hydrolysis due to heat or a change in pH medium encountered in oral environment (Hazardous Chemicals, 2015).

BP-A molecules are linked by ester bonds which are susceptible to hydrolysis when exposed to high temperatures or acidic and basic media leading to BP-A leakage from polyvinyl chloride, polystyrene, phthalates and polycarbonate plastics (Welshons *et al*., 2006).

Recent studies correlate serum and/or urine BP-A levels with various diseases, health outcomes and medical conditions such as diabetes (Shankar *et al*., 2011), cardiovascular diseases (Melzer *et al.*

In this issue

2010), carcinogenic risk (Vandenberg *et al*., 2009), premature deliveries and breast cancer (Dodds *et al.,* 1936; Cantonwine *et al.,* 2010), lowered semen quality and sperm DNA damage in males (Meeker *et al.,* 2010; Li *et al.,* 2011) as well as childhood obesity and altered pubertal development (Howdeshell *et al.,* 1999) (Honma *et al.,* 2002). Although BP-A has a short (5-6h) biological half-life, continuous exposure should be taken into consideration since it is an endocrine disrupting agent (Tinne *et al.,* 2012).

Bisphenol A has been detected in varied types of media including air, municipal water, soil, sediments and food items. Thus, people can be exposed to BP-A through different sources. Although the oral route is thought to be the main source of BP-A exposure, inhalation and dermal routes are also possible (Zalko *et al.,* 2011) (Biedermann *et al.,* 2010). Orally, BP-A goes through first-pass metabolism in the liver, after absorption, by cytochromes CYP450, mainly the CYP2C subfamily. Bisphenol A-glucuronide is the major metabolite in human hepatocytes because it is metabolised by glucuronidation, phase II metabolism, and excreted in the urine (Tinne *et al.,* 2012).

Plastic toys are considered to be a major source of BP-A during childhood as most such toys are made of polyvinyl chloride and polystyrene plastics; nevertheless toy manufacturers have never precisely stated leakage risks or appropriate storage conditions for their plastic products. In 2012 the FDA started to ban BP-A-containing resins in babies' feeding bottles and spill-proof cups due to their potential harmful effects. Thus it became a major concern for healthcare providers. According to the European Food Safety Authority (EFSA), the tolerable daily intake of BP-A should not exceed 50 µg/ Kg body weight/day (Beverly *et al.,* 2011). Different analytical methods have been established for precise and accurate measurement of BP-A levels.

Some studies have detected high levels of urinary BP-A in school children, since they are always in contact with plastic toys either by touching and /or sucking. A study performed on 55 infants receiving care in neonatal intensive care unit (NICU) showed that infants who required 4 or more medical devices had higher BP-A levels than those who required 3 or fewer devices (Susan *et al.,* 2013).

It is known that gonadal hormones can be affected by exogenous endocrine disrupting chemicals such as BP-A. Such disruption has a greater effect in childhood due to the immaturity of the endocrine system. Several studies have linked BP-A exposure to chronic conditions such as diabetes, obesity, neurobehavioral deficits or diseases and male reproductive disorders, as well as the hormone dependent cancers of the breast, prostate and ovary. BP-A was shown to exhibit a weak estrogenic activity and binds to androgen and thyroid hormone receptors which can cause disrupting effects on thyroid hormone production and signaling. John *et al., (*2011) observed a significant decrease in T4 and TSH levels associated with high urinary BP-A levels.

A cross-sectional study (Leonardo *et al.,* 2012) performed on 2838 randomly selected participants aged from 6 -19y showed a direct relation between BMI and BP-A urinary concentration. Thus, BP-A has a potential role in increased body weight and obesity. Moreover, BP-A was able to mimic the effect of 17β-estradiol (E_2) on blood glucose homeostasis in mice and therefore may be a contributing factor in diabetes development (Alonso-Magdalena *et al.,* 2005). Although BP-A has a greater effect during childhood, few studies have measured BP-A levels in infants or children (Hui *et al.,* 2015).

Experimental Methods

A method was established at the laboratories of the Pharmaceutical Chemistry Department, Faculty of Pharmacy, Kuwait University to measure BP-A in plastic toys (tiger toy, small doll, large doll, 4 Lego blocks) and bottled drinking water using an ultra-pressure liquid chromatography coupled with ultra-violet detector (UPLC-UV).

Isocratic elution was carried out with a mobile phase comprised of filtered and degassed 0.1% w/v formic acid in water (pH 4) and acetonitrile in proportion of 40:60 v/v and pumped at a flow rate of 0.1 ml/min. Column temperature was set at 45ºC and samples were analyzed at a wavelength of 280 nm and were injected at 10 µl injection volume. Waters® Acquity UPLC system with Binary Solvent Manager, Sample Manager and UV detector, Waters® Acquity UPLC BEH C18, 1.7 um, 2.1 x 50 mm analytical column were used for analysis and method validation. Empower® software was used for data processing and reporting.

BP-A was simply extracted by dipping each plastic toy and drinking bottled water in 1 L of HPLC grade water and 1 ml was drawn using a Gilson pipette and placed in 2 ml glass screw thread vials for analysis. Analysis and extraction were done after storing plastic toys and drinking bottled water at 45

°C for four days. A stock solution containing 1 ppm of BP-A dissolved in HPLC grade water was used as a standard

RESULTS

The linearity of the method was established with five concentrations ranging from 12 ppb to 600 ppb. Plastic toys and drinking bottled water were stored at 45 °C for four days and the amount of leached BP-A analyzed (Table 1).

Samples were also analyzed in the mass spectrometer to confirm that the peaks detected by UPLC-UV were indeed BP-A (Fig 2).

Other peaks were eluted prior to the peak of interest which are believed to be due to migration of different plasticizers from polycarbonate plastics, which needs further study to be identified and quantified. Blanks were analyzed between sample injections to ensure that the system was free from any BP -A contamination. Linearity of detector response

Table 1. Analysis of BP-A levels in six randomly selected plastic products (four toys) and two brands of bottled drinking water.

Item	BP-A levels after 12 h exposure at 45 °C	BP-A levels after 4 days exposure at 45 °C
Tiger toy	97.1 ppb	239 ppb
Small doll	detection below LOQ	3 ppb
Big doll	detection below LOQ	4 ppb
Lego blocks	1.3 ppb	30 ppb
bottled drinking water 1	50 ppb	59 ppb
bottled drinking water 2	ND	ND

Abbreviations
ND: Not detected, ppb: parts per billion, LOQ: Limit of quantification

Fig 1 below shows, respectively, the chromatograms obtained for BP-A levels in the tiger toy and the Lego blocks after storage at 45 °C for four days.

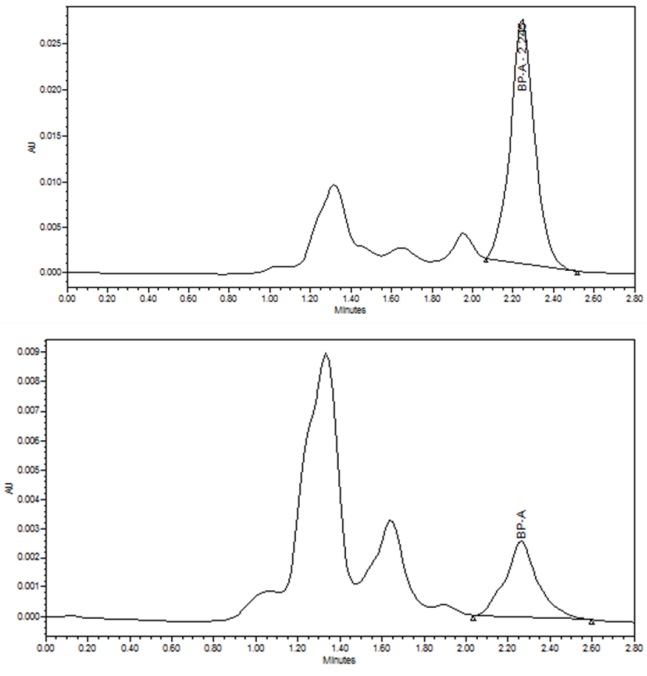


Fig 1. UPLC-UV analysis of BP-A levels in two toys stored at 45°C for 4 days.

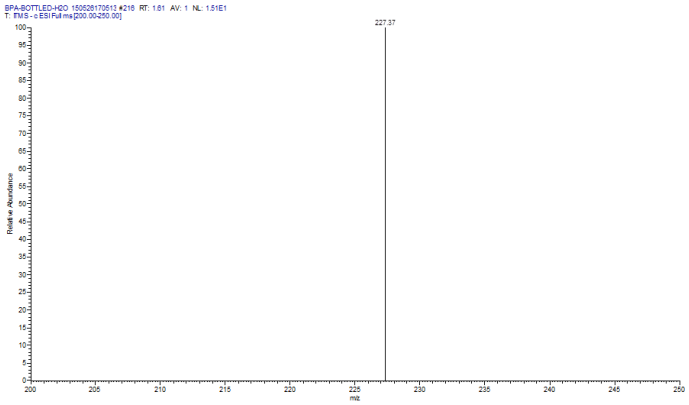


Fig 2. MS spectrum of BP- A

was achieved with r^2 value of 0.9999 by analyzing five diluted concentrations (12, 240, 360, 480 and 600 ppb) of the stock solution.

The extracted BP-A levels were quantified using the calibration curve generated during standard analysis. In the current study, BP-A was found in all randomly selected toys and one out of two randomly selected bottled drinking water. The detected amounts are below the daily tolerated dose stated by the EFSA. However, the EFSA criteria have been questioned as epidemiological and animal investiga-

tions continue to demonstrate the harmful effects of BP-A daily intake at doses below the current reference daily tolerated dose (Richter *et al.,* 2007; Vandenberg *et al*., 2009). 1.3-1.8 ng/ml of urinary BP-A concentration range was found to have externalizing and internalizing behavioral effects in 2y-old children (Braun *et al.,* 2009). Although the highest estimated BP-A exposure in childhood is believed to be due to polycarbonate plastic bottles, canned foods with polycarbonate coating, consumption of beverages lined with polycarbonate bottles and microwaved foodstuff (WHO, 2010; LaKind and Naiman, 2011), toys are persistent and additive pathways of BP-A exposure (Kim *et al.,* 2003).

The drinking water bottles selected in the current study were made from polyethylene terephthalate (PET) resin of the polyester family, which is considered to be safe and BP-A free (Shao *et al.,* 2005). However, Tokunaga *et al.,* (2008) indicated an average concentration range of 3-10 ng/L of BP-A in drinking water bottles made from PET. Therefore, the raw material and the technology used in plastic bottle production may contribute significantly to the BP-A level present in drinking water (Amiridou *et al.,* 2011). Surprisingly, in the present study, 0.59 ppb of BP-A was detected by the established method in one of the randomly selected drinking water bottles, which may be indicative of poor quality of raw materials and/or poor production technology.

Thus, multiple sources of BP-A exposure can increase levels of this potentially toxic compound particularly in children, which may lead to serious health complications. Our study agrees with other results (Amiridou *et al.,* 2011) indicating that BP-A leakage increases with long storage time and elevated temperature. Note that UPLC-MS-MS technique remains the most efficient compared to other techniques used in BP-A detection and quantitation.

HOW TO REDUCE BP-A EXPOSURE

BP-A is involved in every aspect of our daily life, which makes it nearly impossible to avoid being exposed to it. However, many health organisations recommend ways of trying to reduce the exposure. FDA recommendations are to breastfeed infants instead of using infant milk formula because it will contain less BP-A especially when the feeding mother watches her diet and avoids canned food. In addition, discarding scratched plastic baby bottles, infant feeding cups and other plastic food containers is highly recommended because scratched plastic leaks more BP-A than unscratched plastic.

FDA also recommends avoiding use of boiled or very hot water in plastic bottles since heat enhances BP-A leakage from plastic. They advise boiling water in a BP-A free container then mixing it with powdered infant formula and allowing it to cool to hand-hot heat prior to putting it in a plastic feeding bottle. FDA also advises to only use dishwasher safe and microwave safe containers.

Generally, plastics with recycle codes 1, 2, 4, 5, and 6 are unlikely to contain BP-A, while plastics with recycle codes 3 and 7 are more likely to contain BP-A. FDA urges manufacturers to develop alternatives to BP-A and support any effort to replace or minimize BP-A use in food cans linings (FDA, 2015).

Moreover, the National Institute of Environmental Health Sciences (NIH) has recommended to reduce canned food consumption It encourages glass, porcelain, stainless steel containers and BP-A free baby bottle usage. Yet, in Kuwait, many of these recommendations are absent and there are no laws or regulations regarding plastic usage and storing conditions (NIH, 2015).

CONCLUSION

BP-A is an endocrine disrupter whose exposure has been linked to adverse health conditions as well as to several diseases. The occurrence of BP-A in plastics has raised many health concerns. Many research centers have developed extraction and analysis methods for various types of samples that may contain and leach out BP-A. The UPLC-MS-MS technique was found to be superior in terms of sensitivity, selectivity and shortness of retention time when compared to other techniques. Heat is a major factor for BP-A leakage from plastics. In our study, BP-A was detected in all randomly selected plastic toys and one out of

two randomly selected PET bottles of drinking water. Therefore, imported mineral water should be filled in a glass container rather than plastics due to the high temperatures in Kuwait. Moreover, toy manufacturers should use BP-A free plastics or clearly specify storage conditions of their plastic products in order to prevent potential health risks resulting from BP-A leaching.

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TEST YOUR KNOWLEDGE

1)Which of the following plastics-containing BP-A is used in manufacturing intravenous fluid bags, respiratory masks and endotracheal tubes?
a) Polycarbonate
b) Polysulfone
c) Polycrylates
d) Polyetherimide
e) All of the above

2) *Which of the following medical conditions is not associated with exposure to high levels of BP-A?*
a) Diabetes
b) Cardiovascular disease
c) Epilepsy
d) Childhood obesity
e) Cancer

3) *Which of the following recycle codes indicate plastics that are more likely to contain BP-A?*
a) 1
b) 2
c) 3
d) 4
e) All of the above

Answers on back page

Is there a problem?
A child weighing 25 kg was given the following prescription for a fungal skin infection. Is there any major error with the prescription?

BMX HOSPITAL

Patient Name: Faisal Ali Age: 8 years
Address: Street No.28
Rx
Ketoconazole tablets
200 mg once daily
Send one pack
Dr. Roy
Signature Date: 5/09/15

Answer (Prescription Exercise)
The dose is incorrect. For a child weighing less than 30 kg the dose should be 100 mg once daily.
Source: British National Formulary

TOPICAL ISSUES AND CONTROVERSIES

New medical ethics issues in cancer gene sequencing

Researchers are wrestling with what to look for in genomic studies, how to handle the resulting information and whether to contact patients for additional consent before genomic studies. Clinicians want to know more about what constitutes a "medically actionable" gene variant, how to respect patient autonomy without shirking ethical responsibility, and what to do about potential genetic discrimination and the threats to privacy posed by electronic medical records. Patients may not be sure how much of this information they want to know and may not have access to adequate genetic counseling.

The rise of the incidentalome

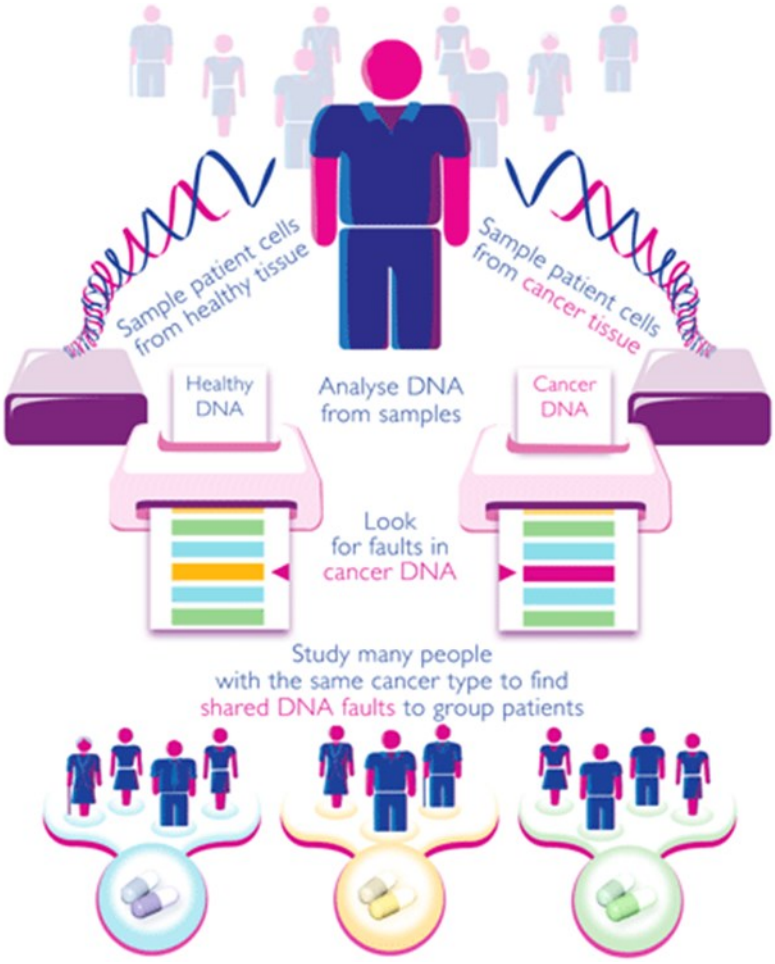
Cancer genome studies are typically done by sequencing both a tumor cell and a normal cell from the same patient. Subtracting the normal (germline) sequence from the tumor cell sequence reveals the tumor genome.

Once a genome is sequenced, the genomic information immediately becomes electronic information and there are problems of privacy protecting. A viewpoint essay was published in the July 24/31 issue of *JAMA* (2013;310:369-370) that addressed the implications of balancing secondary genomic findings with patient autonomy.

Researchers puzzle over what to look for

Genomics researchers are debating whether to set limits on what they look for to avoid the ethical and logistical complications associated with having "too much information" about an individual patient. This represents something of a pushback against the 2013

American College of Medical Genetics and Genomics (ACMG) recommendation on incidental findings, which states that laboratories "seek and report" 57 specific genetic variants in all clinical germline exome and genome sequencing, "including the 'normal' of tumor-normal subtractive analyses in all subjects, irrespective of age, but excluding fetal samples." Twenty-three of those mutations pertain to cancer risk.



It is recommended that in retrospective studies, germline variants should not be explicitly defined at the time of tumor genetic analysis, as a way of striking a balance between research goals and protecting patient privacy.

According to experts, optimal interpretation of the cancer genome requires a comparison with the inherited genome, but it is possible to avoid explicit listing of inherited variants. This strategy is justifiable in retrospective genomic research, but is less supportable in the prospective setting. For prospective studies, they recommend discussing disclosure of incidental findings as part of the informed-consent discussion.

Who knows? Who wants to know? And what Is there to know?

Clinicians puzzle over what constitutes a "medically actionable" genetic variant, what and how to tell patients, and how to address genetic privacy issues such as the risk for genetic discrimination. Although the ACMG position is that information about all "medically actionable variants" should be given to the patient, there is no consensus on what constitutes medically actionable. The 2 main types of medically actionable gene variations are those associated with increased risk for cancer or other diseases and those with a pharmacogenomic impact that increases or decreases drug efficacy or adverse effects. There is certainly a need for more empiric information regarding what kind of information patients really want to know and how best to inform their choices.

Steering through a tsunami of genetic information

There will be a tsunami of genetic information in the next few years. Doctors and patients don't understand it. There is a huge need for education of everyone about it. There is a huge shortage of genetic counselors. We are going to have all this information and not know how to process it, how to interpret it, what to give to patients, or how to explain it to them.

This is a challenge for everyone involved in medicine.

Developing personalized medicine depends on researchers being able to access many people's genomes.

The Genetic Information Nondiscrimination Act covers health insurance but does not cover life insurance, disability insurance, or long-term care insurance. If you apply for life insurance, the company is within its right to ask, 'Have you ever undergone a genetic test? Has anyone in your family ever undergone a genetic test? What was the result?' If it included the *BRCA1* breast cancer gene, the company can refuse to insure you or can charge a much higher rate. Genetic discrimination is very real and is a problem.

For prospective research and clinical translation,

the path forward depends on approaches that better define actionable variants and the development of the evidence base and clinical infrastructure to support preference-based disclosure of incidental findings, which will require the creation and evaluation of decision tools and the clinical capacity to provide genomic counseling for which no standards of care exist.

Source: Cancer Gene Sequencing Raises New Medical Ethics Issues. Medscape. Sep 06, 2013.

Patients are harmed by high cancer drug costs

A recent paper showed that the high prices of cancer drugs are harming patients. The forum article received a huge amount of publicity when it was published online in the journal *Blood* and has spurred American politicians to action.

In the past 10 years, there has been a dramatic increase in the price of cancer drugs. The average price was about $5000 before 2000 and by 2005, the average drug price ranged from $30,000 to 50,000, and in 2012, nearly all of the new drugs for cancer are priced over $100,000 in the US. Some of the recent newcomers include 3 drugs for chronic myeloid leukemia (CML) that were launched in 2012: ponatinib (Iclusig, Ariad) which costs $138,000 per year; omacetaxine (Synribo, Teva), which costs $28,000 for induction and $14,000 for a maintenance course; and bosutinib (Bosulif, Pfizer), which costs around $118,000 per year.

In addition, the new CML drugs were entering an already crowded market. Hagop Kantarjian, from the Department of Leukemia at the University of Texas M.D. Anderson Cancer Center in Houston and one of the authors of the paper, cited survival data for CML patients as evidence of the harm that drug prices can do.

In Sweden, where drug therapy is supplied to patients at no cost, the 10-year survival rates are 80%, whereas, in the US, where CML patients have to pay a proportion of the drug costs, leading some to discontinue treatment, the 5-year survival rate is only 60%.

The situation in other countries is even worse: worldwide, only 20% to 30% of all CML patients are taking these drugs; the rest cannot afford them. In many emerging countries, governments cannot afford these drugs, and so the front-line treatment for CML is stem cell transplantation, which is not suitable for all patients and which is associated with early mortality and long-term morbidity.

In their paper, the experts compare the price of CML drugs in different countries around the world- something that has not been done before. There is so much variation in the price of the same drug around the world.

It is clear from this comparison that the cost of these CML drugs is 50% to 100% higher in the US than anywhere else in the world. In the US, medical costs have become a top cause of bankruptcy, and

Estimated Annual Cost of CML Drugs by Country (in US Dollars)

Country	***Imatinib***	***Nilotinib***	***Dasatinib***
Argentina	52,000	73,500	80,000
Australia	46,500	53,500	60,000
Canada	46,500	48,000	62,500
China	46,500	75,000	61,500
Germany	54,000	60,000	90,000
Japan	43,000	55,000	72,000
Mexico	29,000	39,000	49,500
Norway	50,500	61,000	82,500
Russia	24,000	48,500	56,500
S Korea	28,500	26,000	22,000
UK	33,500	33,500	48,500
USA	92,000	115,500	123,500

cancer is often the reason. A recent study found that the rate of bankruptcy among those with a cancer diagnosis is double that of the rate in the general population.

One of the solutions suggested is that the initial price of a new cancer drug should be set according to a value-based system, which would take into account several parameters: the benefit in overall or progression-free survival, improvement in quality of life, and the reduction of adverse effects and/or cost when compared with existing therapies.

In their detailed review, the authors discuss the many factors that contribute to the extremely high prices of cancer drugs in the US, which can be 2 to 4 times the price charged for the same drugs in other countries. They also make the point that even within the US, cancer patients undergoing the same treatment are charged differently according to which medical insurance system they are in, and some end up paying substantial amounts for cancer drugs, especially the new oral agents, out of their own pockets. Dr. Kantarjian and colleagues outlined a potential solution, which they believe would result in a justum pretium, a "just price" where the price reflects worth. By encouraging prices based on real value, drugs should become more affordable and their cost less burdensome to patients and they also suggest that pharmaceutical companies will be incentivized to "develop better drugs that everyone can agree really are better."

Oncologists Can Change Prices

That oncologists acting together can make an impact on drug prices is illustrated by the recent case of aflibercept (Zaltrap), for which the manufacturer, Sanofi, cut the price drastically after protests. The company was responding to a protest from oncologists at Memorial Sloan-Kettering who refused to add the new drug to the hospital inventory because it cost twice that of a similar agent, bevacizumab (Avastin), used in the same setting. After the researchers publicized their decision in an op-ed in the New York Times, the company began offering discounts that effectively halved the price of the new drug. However, the discount by Sanofi doesn't really address the problem, because Medicare reimbursement and patient copayments are still based on the higher list price. In other words, hospital and cancer practices would pay less for the drug because of the 50% discount, but the reimbursement would stay the same. This actually might give doctors and hospitals a financial incentive to use aflibercept. Nevertheless, oncologists came together, took action, and had an impact on drug pricing.

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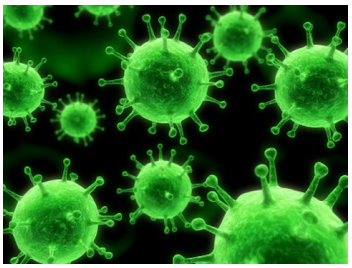
From toxins to therapeutics

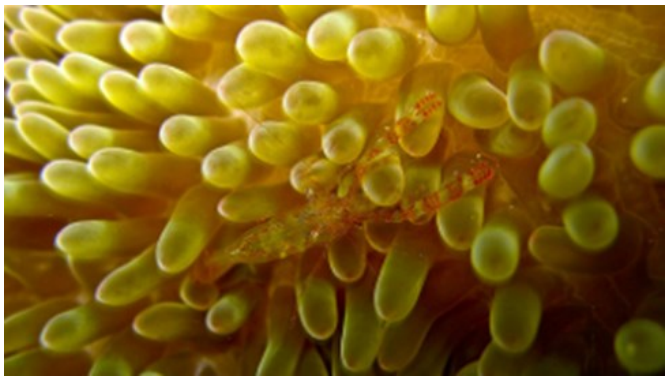


Researchers are finding new drugs for chronic pain and autoimmune diseases by modifying animal venom-derived molecules that target the nervous and immune systems. Animal venoms are a veritable treasure of proteins and peptides fine-tuned by millions of years of evolution to kill or incapacitate both predator and prey. Their high molecular specificity and potency has long made them a promising source of drug candidates. More than 30 years ago, the US FDA approved the first venom-derived drug- a therapy for hypertension, called Capoten, copied from a pit viper venom peptide.

Targeting autoimmunity

The most compelling venom-derived drug currently in development comes from the sun anemone (Stichodactyla helianthus), which lives on reefs in the Caribbean. In the 1990s, a group of physiologists at the University of California, Irvine, showed that one of its toxins, a peptide called ShK, is a potent inhibitor of a T lymphocyte potassium channel called Kv1.3, the upregulation of which is implicated in autoimmune diseases.

To turn ShK into a useful therapeutic, however, the researchers had to make one important change. ShK is very potent on kv1.3 channels, but the big problem is that it blocks another potassium channel called kv1.1, found on neurons. After studying



A Caribbean sun anemone (Stichodactyla helianthus)

ShK's structure and functional properties, they tested almost 400 different synthetic derivatives of the compound. They settled on a version featuring an additional amino acid liked to the compound's N-terminus, which ensures it does not block ion channels on cells other than T lymphocytes. The resulting synthetic peptide- called ShK-186 binds Kv1.3 channels with 100-fold greater potency than Kv1.1 channels, all but eliminating the potential for unforeseen side effects.

They later demonstrated in rodent models of multiple sclerosis (MS) that ShK-186 dramatically reverses paralysis. And importantly, the drug did not broadly suppress the immune system, as treated animals were still able to fight off both chlamydia and influenza.

In December 2012, Seattle-based biotechnology company Kineta completed Phase 1a human trials, testing for the safety of ShK-186 in healthy volunteers. Although the results are yet to be published and there is a long way to go before it hits the clinic, ShK-186 currently holds great promise as a treatment for a range of autoimmune diseases, from MS to lupus and rheumatoid arthritis.

Black mamba (Dendroaspis polylepis)

Fighting pain with venom

The first, and as yet, the only approved venom-derived drug that acts on the nervous system is the painkiller Prialt, a chemically identical version of a peptide isolated from the cone snail (Conus magus). Approved in 2004, Prialt is injected into the fluid around the spine, where it blocks a calcium ion channel in neurons and inhibits the cells' ability to transmit pain signals to the brain.

But there are several promising leads for new venom-derived painkillers. Earlier this year, researchers at the National Center of Scientific Research (CRNS) in Paris announced the discovery of two peptides isolated from black mamba venom that can block neuronal acid-sensing ion channels (ASICs), which play a key role in the pain pathway. In mice, these peptides, dubbed mambalgins, showed potent analgesic effects, as powerful as morphine, with no obvious toxicity and with less tolerance than morphine. Researchers are now developing mambalgins into a human pain therapeutic with the venom-focused pharmaceutical company Theralpha.

Cone snail (Conus magus)

Another painkilling peptide, also under development by Theralpha, is derived from hannalgesin, a neurotoxin isolated from King Cobra (Ophiophagus Hannah) venom. Although the mechanism of action for this peptide, known as THA903, is not yet clear, pre-clinical studies have shown that it has a far stronger analgesic effect than morphine and, crucially, can be taken orally.

Meanwhile, other researchers are continuing to derive potential therapeutics from cone snails. Conus catus, for example, a close relative of Prialt's source C. magus, yields a toxin that the Australia-based company Relevare Pharmaceuticals has developed into an intravenous treatment called Leconotide. The drug blocks the same channel as Prialt and is currently in Phase 1 trials.

These promising drug candidates are likely just the tip of the iceberg, researchers agree. It is estimated that less than 0.1 % of the venom proteome of cone snails- thought to harbour around 100,000 peptides. In other words, we have millions of molecules that are all potential drugs still to be explored.

Source: http://www.the-scientist.com/?articles.view/articleNo/34745/title/From-Toxins-to-Therapeutics/

Debate over "female Viagra"

Seventeen years after Viagra, not a single medicine has been formally approved for sexual problems in women. Now, the makers of a drug that purports to boost a woman's libido by targeting her brain are launching their third attempt to win American government approval, amid a debate over whether there has been a gender bias in the high-stakes field of sexual pharmacology- or a manufactured cure for a medical disease that may not exist.

The U.S. FDA is reviewing new safety data for flibanserin, a once-a day Sprout Pharmaceuticals drug that restores sexual desire in women by "fixing" an imbalance of brain chemicals that drive sexual excitement and inhibition. Unlike Viagra, which is taken on an "as needed" basis before sex, flibanserin must be taken daily.

Twice the FDA has rebuffed flibanserin, dubbed "pink Viagra," over safety and efficacy concerns, leading to charges that the agency is sexist for approving sexual medicines for men, but not for women. Other women's groups are furious for what they see as a hijacking of feminist rhetoric by drug-company orchestrated campaigns designed to put political pressure on regulators to approve a pill for a "hypoactive" sex drive. Some believe that low sexual drive is a significant problem for many women and nothing is available to help women. The executive director of Obstetricians in Canada said that no one is asking to be turned into a teenager again but young, vital active women want to maintain a relationship with their partners and deserve such a solution.

More than 1,300 Canadian women have been involved in tests of flibanserin. The drug was rejected by the FDA in 2010, and again in 2013, over concerns the less-than-overwhelming benefit about one extra "sexually satisfying event" per month, compared to placebo, was outweighed by side effects such as dizziness, nausea, sleepiness hypotensin, and fainting spells.

The FDA is granting Sprout a third hearing after the North Carolina-based company submitted new safety data, including a driving study conducted in Montreal that found women who took flibanserin at bedtime performed no worse the next morning on simulated driving tests, compared with placebo. Flibanserin was originally developed, but never approved, as an antidepressant. Sprout says the drug works on three neurotransmitters - dopamine, norepinephrine and serotonin — that affect sexual desire. It increases dopamine and suppresses serotonin.

Feminists say there is no evidence that women with low sexual desire have abnormal brain chemistry. But Sprout CEO Cindy Whitehead says brain scans show there is something "biologically different" occurring in women with low desire. Sprout has come under fire from some women's groups for financially backing a campaign called "Even the Score." According to their website (eventhescore.org), the count stands at "26-0″ for the number of FDA approved drugs for sexual problems in men, versus those for women.

Opponents to this theory who work against the approval of flibanserin at the FDA, declare that for many women - and men -having little spontaneous sexual desire can be very normal.

On the other hand, Lori Brotto, an associate professor in the department of obstetrics and gynecology at the University of British Columbia who helped develop psychiatry's official criteria for the newly named "female sexual interest/arousal disorder" said no one single factor is behind loss of desire. She said that neurobiology plays a role but sexual desire isn't rooted in an imbalance of neurotransmitters in the brain. She suggested that part of helping women is normalizing the changes that happen with age, stress and mood, and encouraging women to engage in activities that are actually arousing to them.

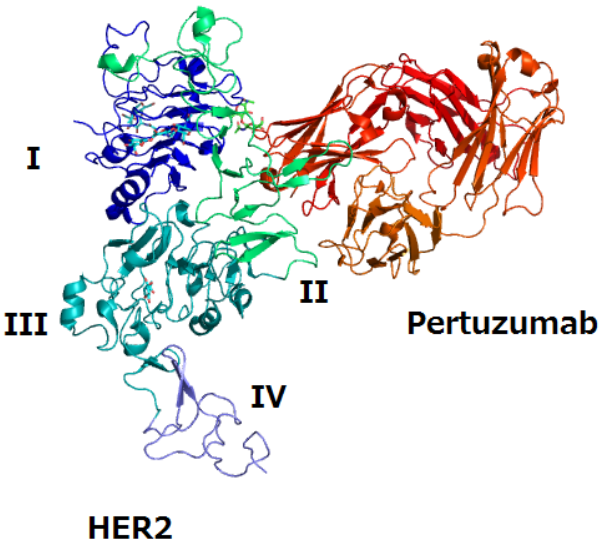
Source: *news.nationalpost.com/.../drug-to-boost-womens-sex-drive*

NEWS from the FDA

Panel backs approval of first neoadjuvant drug for breast cancer

Pertuzumab was set to be approved for the neoadjuvant treatment of breast cancer in the preoperative setting, based on the recommendation of a FDA advisory panel.

At a meeting in September 2013, the FDA's Oncologic Drugs Advisory Committee panel voted 13 -0, with 1 abstention, that treatment with pertuzumab, a human epidermal growth factor receptor 2 (HER2)-targeted monoclonal antibody, had a favorable benefit-to-risk profile as a neoadjuvant treatment in combination with trastuzumab and docetaxel before surgery in patients with locally-advanced, inflammatory, or early-stage breast cancers greater than 2 cm in diameter. The neoadjuvant approach would be part of a complete early breast cancer treatment regimen containing fluorouracil, epirubicin, and cyclophosphamide or carboplatin.



The drug is being reviewed under the accelerated approval process, a mechanism that makes drugs available to fill an un-met medical need in patients with serious diseases.

Historically, the usual sequence of the FDA approvals for breast cancer agents starts with approval for metastatic disease, followed by approval for early-stage disease years later after the results of large studies with long follow-up periods are available.

Pertuzumab, marketed as Perjeta by Genentech, was just approved in 2012 as a first-line treatment for metastatic HER2-positive breast cancer in women who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

Accelerated approvals are based on a surrogate endpoint that is considered "reasonably likely" to predict clinical benefit. Pertuzumab was added to trastuzumab (Herceptin) – another HER2 receptor antagonist – and docetaxel, and was given before surgery to women with HER-2-positive, locally advanced, inflammatory or early-stage breast cancer. The comparator group was patients treated preoperatively with trastuzumab and docetaxel.

The women who received the three-drug neoadjuvant regimen had an 18% improvement in pCR as compared to women given trastuzumab and docetaxel only.

The vote to support the first approval of a drug for the neoadjuvant treatment of breast cancer is a historic moment with the hope that women with earlier stages of breast cancer will live longer and better.

NeoSphere, a randomized study conducted outside of the United States, compared four treatment regimens in 417 women newly diagnosed with locally advanced, inflammatory or operable HER2-positive early breast cancer, with tumors greater than 2 cm, treated for four cycles before surgery. The median tumor size was about 5 cm, and two-thirds were node positive.

Based on the pCR definition used by Genentech (the absence of invasive cancer in the breast), almost 46% of those on the combination of pertuzumab, trastuzumab, and docetaxel reached the primary endpoint, compared with 29% of those on trastuzumab and docetaxel – a statistically significant difference of nearly 17%. Based on the FDA-preferred definition of pCR definition (the absence of invasive cancer in the breast and lymph nodes), the pCR rate was almost 18% higher with the three-drug regimen (39.3% vs. 21.5%).

The FDA considers pCR as "reasonably likely" to predict outcomes in HER2-positive breast cancer.

Genentech also provided results from the TRYPHAENA phase II study that compared three neoadjuvant treatment regimens before surgery; as well as the CLEOPATRA phase III study, the basis of the

2012 approval of trastuzumab. In TRYPHAENA, 225 women with HER2-positive, locally advanced, operable or inflammatory breast cancer, received one of three neoadjuvant treatment regimens. The pCR rates, a secondary endpoint, ranged from about 55% to 64% when pertuzumab was added to trastuzumab and chemotherapy.

CLEOPATRA enrolled 808 women with HER2-positive, locally recurrent, unresectable or metastatic breast cancer previously untreated with a biologic or chemotherapy for metastatic disease. In that trial, pertuzumab in combination with trastuzumab and docetaxel resulted in significant improvements in progression-free survival and overall survival.

The most common adverse events with the three -drug regimen in the NeoSphere study were neutropenia, diarrhea, nausea, fatigue, mucosal inflammation, and rash, according to the company. No unexpected safety signals were observed with the addition of pertuzumab. The addition of pertuzumab did not appear to increase symptomatic cardiac toxicity when added to trastuzumab-based neoadjuvant or metastatic treatment regimens.

The FDA reviewers noted, however, that the rate of left ventricular dysfunction (mostly asymptomatic) was higher with neoadjuvant pertuzumab treatment. Cardiac toxicity appeared to be reversible, however.

Panel member Deborah Armstrong of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, said that there were "some hints of increased cardiac toxicity." She encouraged the company to closely evaluate patients on longer-term pertuzumab in trials for cardiac toxicity.

Genentech has completed enrollment in the confirmatory, phase III APHINITY study, which will compare chemotherapy plus trastuzumab with or without pertuzumab before surgery in about 4,800 patients with HER-2 positive early breast cancer. The patients will be followed for 10 years, and the study will evaluate invasive disease-free survival. Results are expected to be first available in 2016.

Source: http://www.practiceupdate.com/Explore/News/?Id=3208&elsca1=emc_acq_splty-onc&elsca2=email&elsca3=elsevier_oncologystat&elsca4=20130923_top-articles&elsca5=acquisition

FDA cancels approval for bevacizumab in breast metastatic cancer

The US FDA revoked its approval of bevacizumab (Avastin) for the treatment of metastatic breast cancer. The drug costs about $90 000 (£58 000; €68 000) a year and had created about $3.5bn in sales annually for its manufacturer, Genentech.

FDA authorities state that the drug had not been shown to be safe and effective in metastatic breast cancer. A review of studies did not show that the drug extended the lives of women with metastatic breast cancer and women taking bevacizumab risked life threatening side effects such as severe hypertension, bleeding, heart attack, or heart failure, and perforations of the nose, stomach, and intestine.

The European Medicines Agency (EMA) has approved bevacizumab with paclitaxel for treating metastatic breast cancer but the UK's National Institute for Health and Clinical Excellence (NICE) has not recommended its use with taxane drugs as first line treatment for the condition.

The FDA quickly approved bevacizumab for breast cancer in 2008 under its accelerated approval programme while studies were continuing. Those studies showed only a small effect on tumour growth and patients did not live longer or have a better quality of life than those taking standard chemotherapy.

However, in June 2011 an FDA advisory panel recommended the drug be withdrawn but Genentech objected and in public hearings patients pleaded for the drug that they said was keeping them alive.

In 2013 the FDA finally revoked its approval for bevacizumab in breast cancer. The drug, which blocks blood vessel growth to tumours, is still approved for use in colorectal cancer, non-small cell lung cancer, glioblastoma, and renal cancer.

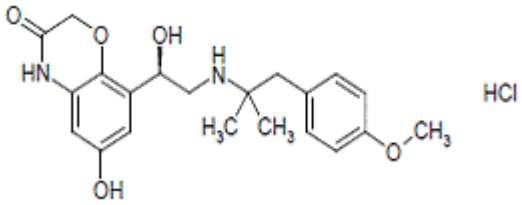
The FDA's decision has no direct effect on health

insurance or medical practice, neither of which it regulates. However, health insurance companies may decide not to reimburse patients for the drug, although doctors may continue to prescribe it "off label" for breast cancer patients. Medicare, the health insurance programme for older people, would continue to pay for the drug but would monitor the situation. Genentech, the manufacturer, was considering conducting a new phase III clinical trial to see which patients might be helped by the drug.

Source: BMJ2011;343:d7684

FDA panel votes in favour of Olodaterol for COPD

The Pulmonary-Allergy Drugs Advisory Committee of the US FDA voted in favour of the data supporting the efficacy, safety and approval of Boehringer Ingelheim's olodaterol, a long-acting beta-agonist, delivered via a metered dose inhaler under the proposed trade name *Striverdi Respimat*.



The proposed indication is for long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. The proposed dose is two 2.5-µg sprays once daily for a total dose of 5 µg olodaterol.

Exercise Tolerance

Boehringer is also seeking FDA approval to make claims in the product label about olodaterol's ability to increase exercise tolerance, increase inspiratory capacity at rest and during exercise, and reduce lung hyperinflation based on decreased functional residual capacity. No COPD treatment currently on the US market makes such claims on their product label.

No decision was reached on the labeling proposal. Some panel members agreed with the FDA analysis that despite a statistically significant 14% improvement in exercise tolerance, as measured in seconds, it was not clear to what degree that difference translated to clinically relevant improvement for patients.

The manufacturer's data came from 7 dose ranging/dose regimen trials (3 in COPD and 4 in asthma), four 48-week trials, and six 6-week trials, 2 of which were focused on exercise. The majority of the trials permitted patients to continue taking usual care background medications, including long-acting anti-muscarinic agents (tiotropium), but not other long-acting beta-agonists.

In contrast to data submitted to FDA for previous bronchodilator treatments, the phase 3 studies for olodaterol included patients with all levels of COPD severity including approximately 10% with very severe disease (Global Obstructive Lung Disease stage IV). Also included were patients with comorbidities, including hypertension in about a third of patients in the phase 3 studies.

The overall treatment effect at 12 weeks for the 5-µg dose was an average 65-mL improvement in trough forced expiratory volume at 1 second and a mean 155-mL improvement in forced expiratory volume at 1 second area under the curve. No additional benefit was seen with the 10-µg dose over the 5-µg dose.

There was a safety signal for neoplasms, with 3 patients (0.3%) in the 10-µg olodaterol group developing small cell lung cancers compared with no patients in the placebo group. Panel members agreed with company officials that the difference may be a result of chance and/or an imbalance in preexisting neoplasms between the 2 groups but urged the FDA to monitor for neoplasms specifically in postmarketing surveillance.

Source: http:www.medscape.comviewarticle/778459?src=wnl_edit_medn_wir&spon=34Medscape Medical News

NEWS from the Faculty of Pharmacy Kuwait University

Changing the landscape of pharmacy education in Kuwait

Coherent with its newly defined vision, mission and values, the Faculty of Pharmacy at Kuwait University is embarking on an ambitious and needed development program to strengthen the pharmaceutical sector in Kuwait. Our vision is to "Be recognized as an outstanding innovative leader in pharmacy education and research, contributing responsibly to the continuous improvement of pharmaceutical services and patient-centered care within our community."

One of the major changes currently under way at the Faculty is the educational portfolio. In addition to the current B.Pharm (5 years) and the M.Pharm (2+ years), we are developing a 2-year add-on PharmD, scheduled to start in September 2016, to improve clinical pharmacy education. The BPharm and the PharmD are then expected to be later merged into a single entry-to practice PharmD. The Faculty is also planning a PhD in pharmaceutical sciences to increase the number of highly qualified personnel in the pharmaceutical sector. The development of new academic programs will incorporate several active-learning approaches as well as an important proportion of experiential learning activities to help students integrate faster within their future work environment.

To support the current workforce, the Faculty will continue to offer a range of continuing professional development (CPD) activities, targeting pharmacists and employees working for the Ministry of Health, community pharmacists, industrial pharmacists and other employees of the pharmaceutical industry that have CPD needs. In partnership with the major stakeholders and current content providers, the new Offices of Consultation, Studies and Training and of Strategic Alliances will be instrumental in expanding the scope of our current lectures and courses.

The scientific research conducted at the Faculty is currently amongst the best at Kuwait University. In recognition of the need for a multidisciplinary approach to modern research, the Faculty intends to consolidate its research activities by establishing specialised Units that will have a "bench to bedside" philosophy in order to bring fundamental ideas closer to therapeutic applications.

Fresh from its recent "Let's practice green" annual campaign and a first experience of a public awareness open day on cancer in February 2015, the Faculty will initiate activities designed to increase its patient outreach and visibility. An example is the recent development of a Medicines Information Center (MIC) to provide a precise, updated service to physicians, pharmacists and other healthcare personnel. In the future, the Faculty plans to have a clinic, to become a national training center for pharmacists to develop pharmaceutical care services, where cognitive services will be offered to health care professionals and patients alike. Its aim will be to optimise the use of medicines for patients having complex medication therapy issues.

Finally, there is a need to expand the scope of practice for pharmacists, to enable future graduates to utilise the full extent of their training for the health and well being of the Kuwaiti population. This has to be done in conjunction with the development of standards of practice that are based on credentials obtained by formal education. The Faculty is participating in this effort in close collaboration with the Ministry of Health and the Kuwait Pharmaceutical Association.

You may be asked to participate in any of those initiatives in the future and we welcome any feedback and suggestions (pmoreau@hsc.edu.kw).

P Moreau,
Dean, Faculty of Pharmacy, Kuwait University

Drug bites

According to the IMS Institute for Healthcare Informatics, a US company that tracks sales at the pharmacy level for drug companies, total drug spending in the US in 2014 was $374 billion, 13% higher than in the previous year.

The most commonly prescribed drugs are used to treat a variety of ailments - from pain relief to high blood pressure and high cholesterol. Prescriptions for the following were close to or exceeded 100 million.

- **Levothyroxine** for treatment of hypothyroidism, a condition in which the thyroid gland doesn't produce enough thyroid hormone. This drug is also used to treat thyroid cancer and to help shrink an enlarged thyroid gland.

- **Hydrocodone/acetaminophen** is America's most popular painkiller used to treat moderate to severe pain. Hydrocodone, a narcotic analgesic, relieves pain through the central nervous system, and is used to stop or prevent coughing. This drug can become habit-forming when used over an extended period of time.

- **Lisinopril** (which used to be sold under the brand names Zestril and Prinivil) is a high blood pressure medication. Its main function is to block chemicals in the body that trigger the tightening of blood vessels. Lisinopril is also used to treat heart failure.

- **Metoprolol**, the generic version of Lopressor, is used to treat high blood pressure and also helps reduce the risk of repeated heart attack. Metoprolol also treats heart failure and heart pain, or angina.

- **Atorvastatin**, the generic of Lipitor, is prescribed to treat high cholesterol and is typically recommended in conjunction with diet changes. This drug is believed to have a variety of benefits, including helping prevent heart attacks and strokes.

Adapted from
https://www.nerdwallet.com/blog/health/2015/06/01/commonly-prescribed-drugs-america/

Answers to: Test your knowledge

Correct answers:
1-e; 2-c; 3-c

The *Kuwait Pharmacy Bulletin* (ISSN 1028-0480) is published quarterly by the Faculty of Pharmacy, Kuwait University, and includes a list of recently approved drugs from the MOH. It aims to provide instructive reviews and topical news items on a range of drug related issues. It is widely distributed free within the university, to hospitals, polyclinics & private pharmacies as well as to other universities within the Gulf & Middle East region.

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