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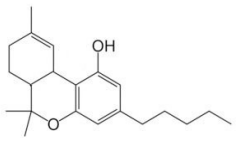
Synthetic cannabinoids found in"Funky Green Stuff™"

Synthetic cannabinoids are drugs of abuse that share common chemical features with natural cannabinoids like Δ^9-tetrahydrocannabinol (Δ^9-THC), and produce similar effects. They are often classified into classical, non-classical and hybrid cannabinoids, aminoalkylindoles and others. Synthetic cannabinoids added to herbal products are difficult to detect using classical methods for cannabis detection mainly because authentic standards are not yet available. Although synthetic cannabinoids are a chemically diverse group of hallucinogens, they can be detected and identified in scent herbal products by means of chromatographic techniques coupled with spectral techniques and NMR. This was demonstrated in this study by performing methanol percolation of the plant material from a bag of a commercial herbal scent called "Funky Green Stuff ™". Several TLC analyses were performed on the dried extract to isolate the main compound(s). Column chromatographic isolation afforded one main pure compound which could be crystallised. NMR and MS spectral analyses identified the isolated pure compound as AB-FUBINACA, a known synthetic cannabinoid, confirming the assumption that a synthetic cannabinoid was present disguised as a herbal scent product.

Introduction

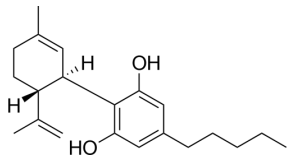
The term designer drug refers to those drugs synthesized from substances that have been subjected to legal controls. However, designer drugs are not subject to the same legal restrictions as their precursors (1). Moreover, they are legal to use, possess and distribute as long as they are marketed for purposes other than for human consumption. As a result, users are often provided little information regarding potential adverse side effects and drug interactions if ingested (2).

While designer drugs comprise a huge number of products, herbal products containing synthetic cannabinoids, more commonly called spice products, have recently become the subject of intense media attention and coverage. They are often advertised as an "incense blend" and labeled "not for human consumption" by their manufactures (3).

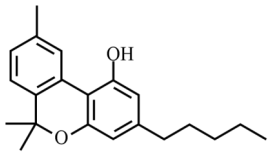


Cannabis is abused as marijuana (the dried plant) or hashish (the resin) for its hallucinogenic effect. Δ^9-tetrahydrocannabinol (Δ^9-THC) is the principle psychoactive component contained in cannabis. This constituent is extracted from the *Cannabis Sativa plant* (Family Cannabaceae).

Cannabis has over 85 active constituents including Δ^9-THC, cannabidiol and cannabinol. Nieiher cannabidiol nor cannabinol produce the euphoria



cannabidiol



cannabinol

caused by Δ^9-THC; cannabidiol has many medical applications, including the treatment of Dravet syndrome, while cannabinol is being used experimentally as an immunosuppressant due to its high affinity to CB_2 receptors.

Synthetic cannabinoids, also called cannabimimetics, affect the endocannabinoid system mainly through binding to CB_1 and CB_2 receptors.

The CB_1 receptors are mainly located in the brain and spinal cord and are responsible for the psychotropic effects of cannabis, whereas the CB_2 receptors are found in the spleen and immune cells mediating immune-modulatory effects (4, 5). Synthetic cannabinoids are chemically unrelated com-

In this issue

pounds that function similarly to Δ^9-THC (6). They produce a number of psychoactive effects including euphoria, sensory perception enhancement, severe memory impairment and hallucinations (7).

They first appeared in Europe in 2004 mixed with herbal products and were advertised as natural herbal incense or room odorisers. Examples are 'Spice Diamond', 'K2', 'Spike', and 'Funky Green Stuff'. Their packaging labels claim that they are pharmacologically active producing cannabis-like effects when consumed. However, these products were found to be a mixture of synthetic cannabinoids with dried pharmacologically inactive herbs (8).

Their popularity is due to the fact that they offer a more potent and more efficacious alternative to natural cannabis. In addition, there are currently no accurate, reliable screening tools to detect them in the human body making them very desirable among those who have to undergo regular drug screenings. Moreover, synthetic cannabinoids are not currently identifiable using conventional forensic blood and urine tests for cannabis (3). Also, they are consumed as an alternative to illegal drugs for experimental drug users, especially teenagers and young people between the ages of 25-40y (6).

These products are mainly smoked or inhaled after vaporization but can also be ingested orally or rectally. Their typical doses are usually less than 1mg due to their much higher potency than Δ^9-THC (6). Their packages are available through internet sources, in head shops, local tobacco shops and petrol stations. Their prices in the US range between $25-40 for approximately 3 g of product, which is considerably more expensive than comparable quantities of marijuana (9)

In December 2008, forensic analysis in Germany and Austria showed that the psychoactive properties of herbal mixtures, such as 'Spice', were the direct result of added synthetic cannabinoids. Investigators discovered that the C8 homologue of the synthetic cannabinoid CP 47,497 was the key active component in the analyzed samples of 'Spice Diamond' (3). Previously, the presence of an aminoalkylindole called JWH-018 was identified in several samples of spice products (10). Subsequent analyses of spice products, in laboratories across Europe, have also confirmed the presence of synthetic cannabinoids (6).

Health risks

Little is known about the metabolism and toxicity of synthetic cannabinoids as these products were only tested in the laboratory (3). They may cause more harm than natural cannabis due to their high affinity and potency, as some synthetic cannabinoids are reported to have 4-5 times the binding affinity to CB_1 receptor as compared to Δ^9-THC (11). Furthermore, the substantial batch variation in the type and amount of the synthetic cannabinoids increases the risk of accidental over-dosing causing significant complications (6). Based on its structure, it is presumed that the synthetic cannabinoid JWH-18 for instance, may be carcinogenic (12). There is high potential for dependence on these compounds (12).

In terms of side effects, it has been found that synthetic cannabinoids produce significant anxiety, tachycardia, palpitations, irritability, seizures and numbness. Some users also experience a number of undesirable side effects including hallucinations, vomiting, paranoia and cramps (13). Ten minutes after smoking a cigarette containing 0.3g of 'Spice Diamond', researchers reported significant reddening of the conjunctivae, dry mouth, increase in pulse rate and alterations in mood and perception (3).

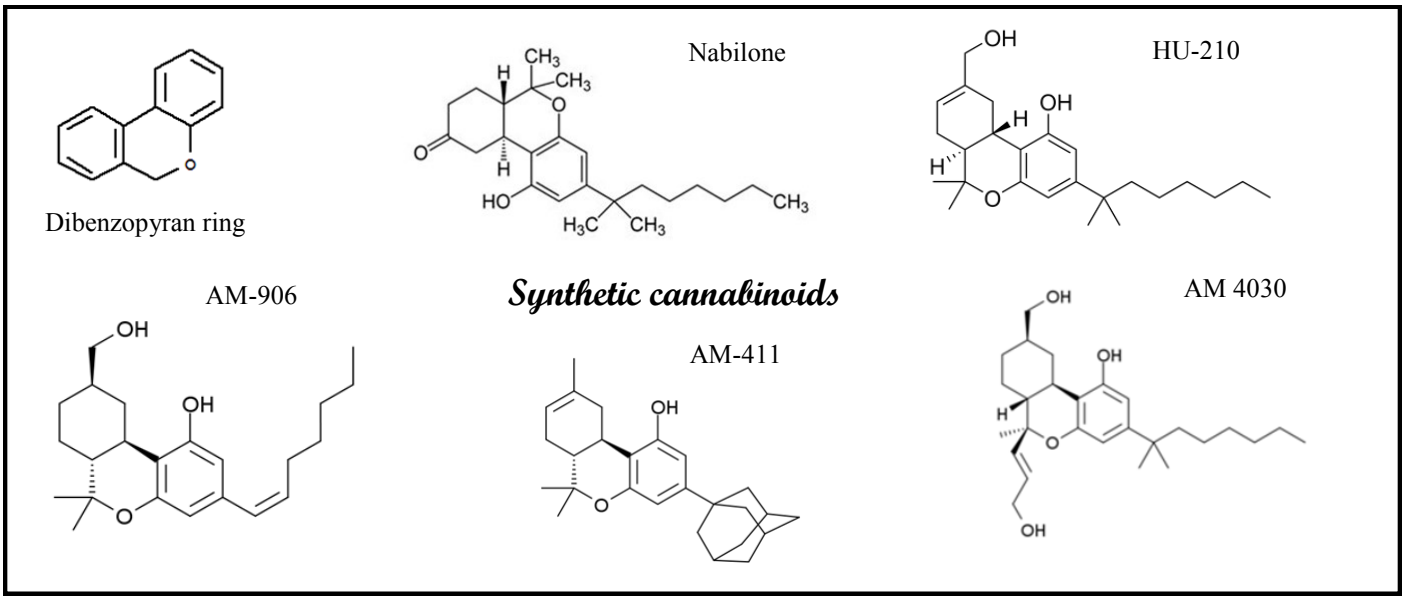
Chemistry

In general, synthetic cannabinoids are lipid-soluble, non-polar, 20-26 carbon small molecules. They are consumed by smoking being fairly volatile. According to the UN Office on Drugs and Crime (UNDOC) (14), these compounds are chemically classified into:

- Classical cannabinoids
- Non-classical cannabinoids: Cyclohexylphenols
  3-arylcyclohexanols

- Hybrid cannabinoids
- Aminoalkylindoles (AAIs):Naphthoylindoles
  Phenylacetylindoles
  Napthylmethylindoles
  Benzoylindoles
- Others: Endocannabinoids and their synthetic analogues
  Diarylpyrazoles
  Derivatives of naphthalene-1-yl Methanone

Classical cannabinoids are Δ^9-THC analogues based on the dibenzopyran ring. These were first developed in the 1960s. Some of them, such as Nabilone, have limited therapeutic use; treatment of chemotherapy-induced nausea and vomiting, just like the Δ^9-THC product, Dronabinol (15). The most common example of this class is HU-210, which has 100 times the potency of Δ^9-THC. Other examples include AM-906, AM-411, and O-1184.



The second group of synthetic cannabinoids is the non-classical cannabinoids which consist of cyclohexylphenols, developed by Pfizer in the 1970s and 1980s, and their *n*-alkyl homologues the 3-arylcyclohexanols. Examples include CP 59,540 and CP 47,497.

Hybrid cannabinoids comprise the third group of synthetic cannabinoids. These are combinations of structural features of classical and non-classical cannabinoids, such as AM-4030.

The fourth and largest group is the aminoalkylindoles. aminoalkylindoles subclasses including napthoylindoles such as JWH-015, JWH-018, JWH-073 and JWH-398, naphthylmethylindoles such as JWH-175, JWH-184 and JWH-185, and naphthoylpyrroles including JWH-030 and JWH-307. Other subclasses are napthylmethylindenes, phenylacetylindoles such as JWH-250 and JWH-251, and benzoylindoles including RCS-4 and AM-694 (6).

Pharmacokinetics & pharmacodynamics

Little is known about the pharmacokinetics and pharmacodynamics of synthetic cannabinoids. When a spice product is smoked, it produces effect within a few minutes due to the rapid absorption *via* lungs and redistribution to other organs such as brain. These maximum concentrations last for 3 h, while the parent compound is still detectable until 48 h after administration (16). However, there is a delay in the absorption following oral consumption due to food intake and digestion activity as well as a loss of drug by first pass metabolism (14). In chronic users, large quantities of these lipophilic com pounds are likely to accumulate in fat-containing compartments after absorption.

Metabolism studies are not easily conducted due to ethical concerns (17). Studies available on the metabolism of synthetic cannabinoids are either based on human liver microsomes or urine analysis from detected users or conducted self-experiments, with aminoalkylindoles being the most studied (18,19,20).

In general, these compounds are excessively metabolised in the liver, leaving no unchanged drug in urine specimens. Aminoalkylindoles are mainly found to be metabolized to monohydroxylated compounds. Other modifications found were multiple

hydroxylation, carboxylation, *N*-dealkylation, dehydrogenation and dihydrodiol formation. Urine samples were found to contain the glucoronide and/or sulfate conjugates (21). An unknown proportion of the aminoalkylindoles is excreted *via* feces. Other compounds, such as CP-47,497-C8, have very low urine metabolite concentrations, resulting in difficulty detecting consumption by analysing urine with standard laboratory equipment.

Legislation & control

What makes the control of spice products so difficult, is that the producers respond so quickly to changes in legislation by making small modifications to the new product launched without affecting its cannabis-like effects (14). For example, after the prohibition of the use and distribution of JWH-018-containing products in Germany, a second generation of herbal products containing the synthetic cannabinoid JWH-073 as an alternative began to fill the market within a month (22).

None of the synthetic cannabinoids are internationally controlled. Each country has its own regulations and control schedules. In January 2011, the US Drug Enforcement Administration (DEA) placed the synthetic cannabinoids JWH-018, JWH -073, JWH-200, CP-47,497 and CP-47, 497-C8 homologues into the schedule I category of the controlled substances act (CSA) (23). In 2009, the German Federal Ministry of Health officially placed all products containing the synthetic cannabinoids JWH-018 and CP-47-497 under the Narcotics Law, which resulted in the ban of production, possession and trade of such products (24).

This approach, however, requires the constant need to schedule different new substances as they continuously appear, which is time consuming. The most important barrier affecting the control of the distribution of these products is the internet, which has already become an unregulated source of drugs, both controlled and uncontrolled, which has immense legal and public health issues. Online vendors of designer drugs can easily evade the laws of individual countries, rendering efforts to regulate such substances ineffective (13).

Therefore, legislators must significantly increase their level of international cooperation in order to combat this increasing phenomenon. In Kuwait, a resolution came into force on March 15, 2015 stating that the importation of any of the products marketed under the name “Spice” or Bath Salt” is banned. However, more work needs to be done to construct the needed tables and more legal work is required as well, to schedule these compounds.

Detection

The abuse of cannabimimetics, including synthetic cannabinoids, cannot be detected using methods for cannabis abuse detection. Reference material for most synthetic cannabinoids is currently unavailable due to the immense variety of these products in the market which makes their reliable identification and quantification difficult.

Herbal products

Generally, identification involves extracting the lipophilic compounds, mainly located on the surface of the plant material, with an organic solvent at room temperature. The extract is then analyzed using chromatographic technique combined with mass spectrometric detection, such as Gas Chromatography-Mass Spectrometry (GC-MS), by comparing it with databases containing spectra of known synthetic cannabinoids. If unknown, their structure can be elucidated using NMR and Mass Spectrometry.

Biological samples

In blood samples, the unchanged compound as well as its metabolites can be extracted using liquid chromatography (LC) (25,26). In terms of oral fluid testing, detection can be performed by direct injection in the LC system but is limited to a few hours after consumption (27,28). If a urine sample is used to detect the target compound, it is essential to know the metabolism of the compound, since no unchanged parent compound is usually found in urine. To detect these metabolites, an enzymatic hydrolysis is usually performed followed by extraction and LC-MS analysis.

However, this method is not practical due to the fast growing number of new compounds. Another option is immunochemical-based detection methods which are cheaper and faster than chromatographic techniques. The only downside is the difficulty of developing such immunoassays due to the great structural variety between these compounds. An Enzyme-Linked Immunosorbent Assay (ELISA) was used to detect the naphthoylindole group of synthetic cannabinoids and their metabolites in urine specimens (29).

Commercial tests for synthetic cannabinoids are becoming available, promising a detection window of 72 h after single use and up to 3 weeks in chronic users. Despite that, a confirmatory analysis with more selective chromatographic techniques is mandatory.

Extraction, purification and identification of potential synthetic cannabinoid(s) in "Funky Green Stuff™"

Acquisition of sample material

One pack of "Funky Green Stuff ™" was provided by the General Administration of Criminal Evidences, Ministry of Interior, Kuwait.

Extraction

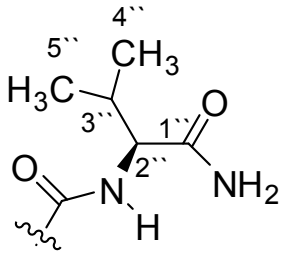
The extraction was performed by repeated steeping of the plant material in methanol overnight, followed by evaporation to dryness of the combined methanol extract *in vacuo* at 38˚C.

Thin layer chromatography

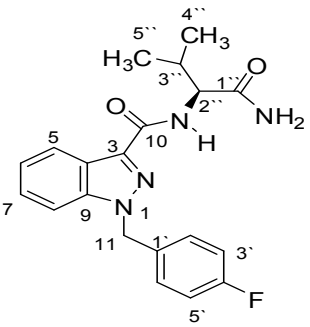
Solvent system A (Toluene: Methanol: Diethylamine; 8: 1.5: 0.5) was found to give a reasonable isolation of the main compound by thin layer chromatography (TLC). This compound was an *N*-containing one as shown by its intense orange color after spraying with Dragendorff's reagent.

Column chromatographic isolation and purification of the potential synthetic cannabinoid

The obtained extract was applied on a flash silica gel column and eluted with a slightly modified version of solvent system A (Toluene: Methanol: Diethyl amine; 8.8: 0.7: 0.5). TLC analysis of selected fractions showed one main UV-active compound. When evaporated to dryness this yielded semi-pure slightly greenish needle-like crystals, abbreviated RA-1. The extract was applied on another flash silica gel column and eluted with solvent system B (Chloroform: Methanol; 9.7: 0.3) yielding one main UV-active compound, which was crystallized out of methanol giving 372 mg (5.2% w/w enrichment ratio) of colorless needles, called RA-2; This was determined to have the composition $C_{20}H_{21}O_2N_4F$. NMR analysis unambiguously supported the presence of a particular side chain (shown below) not frequently seen in the common semisynthetic cannabinoids.



Other NMR data supported the presence of a benzylated indazole nucleus. The identity of this compound was found to be *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-*1H*-indazole -3-carboxamide (abbreviated to AB-FUBINACA) whose structure is shown here.



AB-FUBINACA is a semi-synthetic cannabinoid that was first synthesised in 2009 by Pfizer as a potent CB_1 receptor modulator for potential therapeutic use as an analgesic, but was never pursued for human use. In 2012 it was identified in Japan, along with AB-PINACA, in illegal herbal products (30).

Similarly to Δ^9-THC and other cannabinoids, AB-FUBINACA exhibits its effects through the full agonism of CB_1 and CB_2 receptors, having more selectivity for CB_2 and a 10-fold greater affinity for the CB_1 receptor than JWH-018 (30). Very little data about its toxicity or addiction potential is available. Informal experiments have shown that overdose will cause side effects including heart palpitations, vertigo and sedation at much lower than toxic doses, usually causing the user to fall asleep. In January 2014, the US placed AB-FUBINACA into its Schedule I controlled substances list (31). No AB-FUBINACA detection in "Funky Green Stuff™" has been previously reported.

Products of AB-FUBINACA are usually smoked in doses ranging from less than 1 mg to more than 5 mg. The onset of its psychoactive effects begins 20 min after consumption and lasts 1-2 h, with the peak effect at 30-60 min after consumption.

ADB-FUBINACA is similar to AB-FUBINACA. It contains a *tert*-butyl instead of the isopropyl group. Another similar compound is AB-PINACA that contains a pentyl side chain attached to the indazole ring system instead of the 4-fluorobenzene ring.

Conclusion

AB-FUBINACA, was isolated from a herbal product sold in the markets as an incense product. The market is flooded with similar products marketed as scents or room odorisers. This clearly necessitates the urgent need to increase international co-operation between criminal evidence officials and legislators in order to combat the spread of these products. AB-FUBINCA has not yet been scheduled as a controlled substance in Kuwait, meaning that its use and distribution are still not considered illegal. While mass spectrometry

gives a tentative identification of such compounds, authentic references are only slowly available and not quickly updated. NMR is a useful technique to identify such compounds after isolating them in sufficient quantity.

References

1. Valtar, K., Arrizabalaga, P., & Landry, J.C. (Eds.). (1998). *Designer drugs directory* (1st ed.). Lausanne: Elsevier Science.
2. Schmidt, M., Sharma, A., Schifano, F., & Feinmann, C. (2011). *Forensic Sci Int*, *206*(1-3), 92-97.
3. Auwärter, V., Dresen, S., Weinmann, W., Müller, M., Pütz, & Ferreiros, N. (2009). *J Mass Spectrom*, *44*(5), 832-837.
4. Compton, D., Rice, K., De Costa, B., Razdan, R., Melvin, L., Johnson, M., et al. (1993). *J pharmacol Exp Ther, 265*(1), 218-226.
5. Porter, A. & Felder, C. (2009). *Pharmacol Ther, 90* (1), 45-60.
6. European Monitoring Centre for Drugs and Drug Addiction. (2009). *Understanding the "spice" phenomenon.* EMCDDA, Lisbon. Retrieved April 19, 2015 from http://www.emcdda.europa.eu/publications/thematic-papers/spice
7. Robinson, L., Goonawardena, A.V., Pertwee, R., Hampson, R.E., Platt, B., & Riedel G. (2010). *Behav Brain Res*, *208*, 584-592.
8. United Nations Office on Drugs and Crime. (2013). Identification and analysis of synthetic cannabinoid receptor agonists in seized materials. Retrieved April 19, 2015 from http://www.unodc.org/documents/scientific/STNAR48_Synthetic_Cannabinoids_ENG.pdf
9. Schneir, A., Cullen, J., & Binh, T. (2011). "Spice" girls: Synthetic cannabinoid intoxication. *J Emerg Med*, *40*(3), 296-299.
10. Steup, C. (2008), 'Untersuchung des Handelsproduktes "Spice"', THC Pharm GmbH, 30 December 2008.
11. Uchiyama, N., Kawamura, M, Kikura-Hanajari, R., & Goda, Y. (2010). Identification and quantitation of two cannabimimetic phenylacetylindoles JWH-251 and JWH-250, and four cannabimimetic naphthoylindoles JWH-081, JWH-015, JWH-200, and JWH-073 as designer drugs in illegal products. *Forensic Toxicology, 29*(1), 25-37.
12. Vardakou, I., Pistos, C., & Spiliopoulou, C. (2010). *Toxicol Lett, 197*(3), 157-162.
13. Schifano, F., Corazza, O., Deluca, P., Davey, Z., Di Furia, L., Farre, M., et al. (2009). *Int J Culture Mental Health, 2*(2), 137-144.
14. United Nations Office on Drugs and Crime. (2011). Synthetic cannabinoids in herbal products. Retrieved April 19, 2015 from http://www.unodc.org/documents/scientific/Synthetic_Cannabinoids.pdf
15. Advisory Council on the Misuse of Drugs. (2009). Consideration of the major cannabinoid agonists. Retrieved April 27, 2015 from https://www.gov.uk/government/publications/acmd-report-on-the-major-cannabinoid-agonists
16. Teske, J., Weller, J., Fieguth, A., Rothämel, T., Schulz, Y., & Tröger, H. (2010). *J Chromat B Analyt Technol Biomed Life Sci*, *878*(27), 2659-2663.
17. De Brabanter, N., Deventera, K., Stoveb, V., & Van Eenooa, P. (2013). *Proc Belgian Royal Acad Med, 2*,209-225.
18. Sobolevsky, T., Prasolov, I., & Rodchenkov, G. (2012). *Drug Test Anal, 4*(10), 745-753
19. Kim, U., Jin, M., Lee, J., Han, S., In, M., & Yoo, H. (2012). *J Pharm Biomed Anal*, *64-65*, 26-34.
20. Zhang, Q., Ma, P., Cole, R., & Wang, G. (2006). *Anal Bioanal Chem*, *386*(5), 1345-1355.
21. De Brabanter, N., Esposito, S., Geldof, L., Lootens, L., Meuleman, P., & Leroux-Roels, G. et al. (2013). *Forensic Toxicology*, *31*(2), 212-222.
22. Lindigkeit, R., Boehme, A., Eiserloh, I., Luebbecke, M., Wiggermann, M., Ernst, L., et al. (2009). *Forensic Sci Int*, *191*, 58-63.
23. Drug Enforcement Administration. (2011). Scheduling update. *Microgram Bull, 44*(3), 1-30.
24. Zimmerman, U., Winkelmann, P., Pilhatsch, M., Nees, J., Spanagel, R., & Schulz, K. (2009). *Dtsch Ärztebl Int, 106*(27), 464-467.
25. Dresen, S., Kneisel, S., Weinmann, W., Zimmermann, R., & Auwärter, V. (2011). *J Mass Spectrom*, *46*(2), 163-171.
26. Kacinko, S., Xu, A., Homan, J., McMullin, M., Warrington, D., & Logan, B. (2011). *J Anal Toxicol*, *35*(7), 386-393.
27. Strano-Rossi, S., Anzillotti, L., Castrignanò, E., Romolo, F., & Chiarotti, M. (2012). *J Chromatogr A*, *1258*, 37-42.
28. Kneisel, S., Speck, M., Moosmann, B., Corneillie, T., Butlin, N., & Auwärter, V. (2013). *Anal Bioanal Chem*, *405*(14), 4691-4706.
29. Arntson, A., Ofsa, B., Lancaster, D., Simon, J., McMullin, M., & Logan, B. (2013). *J Anal Toxicol*, *37* (5), 284-290.
30. Uchiyama, N., Matsuda, S., Wakana, D., Kikura-Hanajiri, R., & Goda, Y. (2012). *Forensic Toxicology*, *31*(1), 93-100.
31. Behonick, G., Shanks, K., Firchau, D., Mathur, G., Lynch, C., & Nashelsky, M., et al. (2014). *J Anal Toxicol*, *38*(8), 559-562.

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TEST YOUR KNOWLEDGE

Answers to MCQs on back page

1) ***Which of the following is a non-classical cannabinoid?***

A. Diarylpyrazoles
B. Phenylacetylindoles
C. Cyclohexylphenols
D. Methanone
E. Benzoylindoles

2) ***Which of the following are Δ^9-THC analogues based on the dibenzopyran ring?***

A. Hybrid cannabinoids
B. Endocannabinoids and their synthetic analogues
C. Derivatives of naphthalene-1-yl
D. Classical cannabinoids
E. Methanone

3) ***Aminoalkylindoles are metabolised by:***

A. Multiple hydroxylation
B. Carboxylation
C. *N*-dealkylation
D. Dehydrogenation
E. All of the above

Prescription Exercise

Is there a problem?

A 56 year old male patient was given the following prescription for respiratory tract infection. The patient also uses warfarin tablets. Is there any major error with the prescription?

BMX HOSPITAL

Patient Name: Ali Mohammad Age: 56 years
Address: Street No.14

Rx

Azithromycin tablets
500 mg once daily x 3 days
Send one pack

Dr. Ahmad
Signature Date: 18/06/15

Answer (Prescription Exercise)

There will be a potentially serious interaction between warfarin and azithromycin, where the anticoagulant effect of warfarin is enhanced.

Source: British National Formulary

TOPICAL ISSUES AND CONTROVERSIES

Will genetically modified insects help stop disease?

Historically, malaria and dengue control strategies have incorporated insect population control using insecticides, but in recent years, researchers have turned to genetic engineering. By developing mosquitoes that don't carry such pathogens, researchers hope to stop disease spread.

Culling insects

Researchers creating genetically modified (GM) insects generally have one of two goals, which some experts call them as the 'bite, no-bite' strategies. "Bite" strategies modify the insects in such a way to prevent disease transmission to humans, whereas "no-bite" strategies aim to reduce or eliminate insect populations altogether, by, for example, rendering them incapable of producing viable offspring.

A similar strategy, known as the sterile insect technique (SIT), has been used to successfully shrink populations of tsetse flies, which carry the parasite that causes sleeping sickness. In SIT, male insects are sterilized through irradiation, then released into the wild, where they breed with wild females, but produce no offspring, thereby cutting the size of the next generation. By regularly releasing enough sterile males, officials can drastically reduce the number of disease-carrying insects. Using genetic engineering could streamline the SIT strategy.

In 2002, a method was developed called RIDL-

release of insects carrying a dominant lethal allele. Aedes aegytpi, the primary carriers of dengue fever, was modified to express a lethal toxin as larvae—but only when not exposed to the antibiotic tetracycline. A diet of tetracycline-rich food allows GM insects to develop normally in the lab, then released into the wild where there is no tetracycline, and progeny inheriting the toxin gene will be killed before adulthood.

The same year, the company Oxitec was formed to implement modified mosquitoes in the field. To date, Oxitec has collaborated with governments in the Cayman Islands, Malaysia, and Brazil to begin releasing mosquitoes in dengue-plagued areas. Just last year, they reported 80 percent mosquito suppression in the Caymans, and the Brazilian trial is ongoing.

The University of Oxford and Imperial College London are also developing a similar tetracycline-based *"no-bite" strategy* that renders females flightless. And another collaboration between researchers at the California Institute of Technology and Imperial College London is developing GM males, called "Semele," which carry a toxin that kills wild females upon mating. These techniques have yet to be tested in the field.

Disease-free mosquitoes

Some researchers are developing mosquitoes to express anti-malaria peptides and enzymes that inhibit parasite development, for example. Others, are targeting even earlier stages of infection, engineering mosquitoes to express mouse-derived antibodies that block Plasmodium from ever invading a mosquito's tissues.

Researchers at Johns Hopkins University (JHU) are trying a different tack-*tweaking mosquitoes' own immune systems*. The few parasites resilient enough to evade a mosquito's immune system are the ones that transmit disease, but it was suspected that if the natural immune response of a mosquito is boosted, maybe complete resistance could be achieved.

Transgenic Anopheles mosquitoes have already been developed that, better resisted Plasmodium infection, with little cost to longevity and fecundity, and the researchers are currently working to devise similar strategies to combat dengue in A. aegypti mosquitoes as well.

GM versus wild

The success of both bite and no-bite strategies depends on the ability of the GM mosquitoes to spread through the wild population. When a GM mosquito mates with a wild mosquito, only some of the offspring will carry the new transgenic resistance genes. To ensure that transgenic genes are pushed into wild populations, scientists are developing "gene drive" strategies that guarantee the offspring of a GM-wild pairing will carry the new resistance genes.

While GM males carry a toxin that kills wild females, researchers have also developed GM females that carry an antidote. Thus, male GM mosquitoes only produce offspring with GM females—which are guaranteed to express the GM traits—while killing off wild females to reduce the wild type population.

Another promising gene drive method, not yet tested in mosquitoes, uses a genetic element called Medea, a maternally-derived microRNA that silences expression of a protein important for embryo development, combined with a gene that rescues offspring. If transgenic female fruit flies mate with non-transgenic males, only those progeny that inherited Medea from their mother survive to adulthood. By pairing Medea with transgenic genes of interest, such as those that confer malaria resistance to mosquitoes, scientists hope to quickly propagate the transgenes in insect populations.

Yet another method under development relies on a homing endonuclease called I-SceI. Homing endonuclease genes (HEGs) are selfish genetic elements that can spread themselves to homologous chromosomes, converting heterozygote carriers to homozygotes that must pass on the HEG. Indeed, when researchers engineered Anopheles gambiae mosquitoes to carry I-Scel, they found that it spread quickly through caged populations. The next step is to embed transgenic genes into I-Scel, which the researchers hope will ensure their fast spread as well.

With so many different disease-controlling GM mosquitoes in late-stage development, it is predicted that the techniques will be put into field testing and possible practice in the next 5 years or so.

Source:
http://www.the-scientist.com//?articles.view/articleNo/34005/

Cancer clinical trials of the future

There is a significant change in the fundamental structure of cancer clinical trials, as the emphasis begins to shift from large-scale studies of relatively unselected patients to smaller studies testing more narrowly targeted therapies in molecularly characterized populations. However, the ability to select sub-groups of patients for study has been severely curtailed by a still-limited knowledge of human cancer biology. This is rapidly changing, due to advances in genomics and comprehensive cancer biology research over the last decade.

Large-scale efforts, such as The Cancer Genome Atlas, are comprehensively defining many of the crucial molecular characteristics of human malignancies by illuminating genetic alterations that are clinically and biologically important, and which, by virtue of their functional roles, are viable targets for cancer treatment. At the same time, the ability to design small-molecule inhibitors of specific cancer targets is rapidly accelerating.

In 2011, two new agents exemplified the power of these trends: crizotinib was approved for the treatment of lung cancers that harbor a specific mutation in the ALK gene, and vemurafenib was approved for the treatment of melanomas with a specific *BRAF* mutation.

Clinical trials are being transformed by these trends. It is inevitable that there will be a rise in the number of trials that incorporate molecular tumor testing prior to treatment, with treatment selection informed by the molecular features of each individual's cancer. Such personalized trials have the potential to yield better outcomes by increasing the probability of response and to employ less toxic therapies by increasingly targeting cancer-specific functions, rather than normal proliferative functions.

Smaller and more precise trials

To the extent that targeted therapies will prove more effective when given to selected patients, clinical trials should get dramatically smaller. Trial size is largely driven by how effective the treatment is expected to be, so fewer participants are needed when the therapeutic benefit is larger. But the promise of smaller trials will not to be universal; for example, when two targeted agents are compared to one another in the same molecularly selected population, the differences in efficacy may be small and larger trials will be required.

Smaller trials may not necessarily move faster or be easier to complete, as they will require the "right patients," who may be hard to find. Today, molecular characterization of tumors is often done as part of the screening process for each trial. Many, and sometimes most, of the patients prove ineligible, making this approach frustrating and difficult to carry out. It would be better to make comprehensive molecular characterization of tumors a routine part of establishing a patient's eligibility for a range of therapies.

New challenges

For rare targets that are present in a minority of cases across many different types of cancers, one will have to consider clinical trials that include a number of different cancers. There are many design pitfalls to such trials, chiefly the additional clinical and molecular heterogeneity introduced by the inclusion of more than one cancer type. It will inevitably make sense in some settings to select patients who share a particular tumor biology, regardless of the tissue of origin.

Another major challenge is how to combine targeted therapies to improve clinical outcomes. To date, targeted therapies have not been able to cure advanced solid tumors. Clinical benefits, while sometimes quite impressive when compared to marginally effective treatments, still fall far short. It stands to reason that redundant survival and growth pathways enable tumors to overcome therapies that inhibit a single target. The simultaneous inhibition of relevant redundant pathways may yield dramatically better results, but will also dramatically increase the complexity of molecularly personalized clinical trials.

Fewer than 5% of adult cancer patients participate in a clinical trial. To carry out meaningful clinical trials in the future, that number must increase. This will be most important for treatments that target relatively rare mutations.

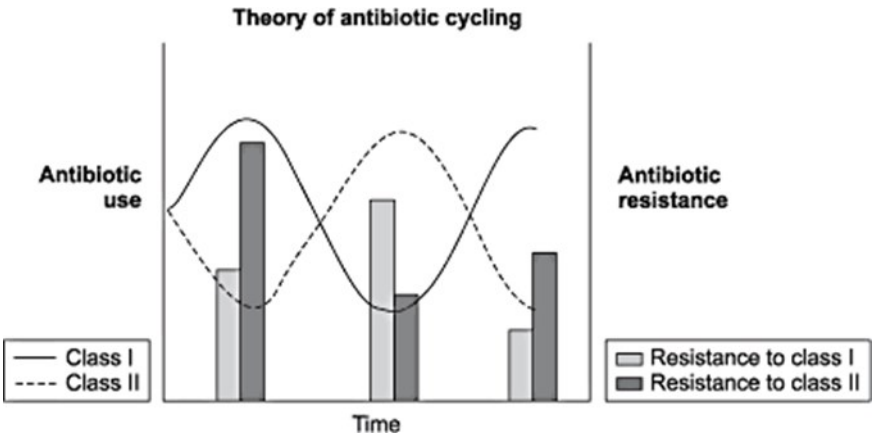
Source:
http://www.the-scientist.com/?articles.view/articleNo/34761/title/Cancer-Clinical-Trials-of-Tomorrow/

Antibiotic cycling could help clinicians battle simultaneously both illness and resistance

The employment of a treatment framework in which clinicians administer different drugs in strategic succession could both treat bacterial infections and select against the development of resistance.

This new framework, which the researchers call collateral sensitivity cycling, could also help curb unnecessary antibiotic use, which is known to contribute to the emergence of *drug-resistant superbugs*.

The idea of alternating antibiotics to both beat bacterial infections and outsmart pathogens on the path to acquiring resistance has circulated in the minds of microbiologists for decades, but clinical data to date have been unconvincing. According to researchers, the thought behind traditional drug cycling is that if you alternate between drugs, you alternate between selection pressures, so if you don't have the selection pressure for resistance, then resistance will disappear. Although this type of traditional drug cycling has at times been shown to be advantageous, at other times it has shown to have no effect at all.



Evans & Sawyer, Drugs Today 2003, 39(9): 733

For the present study, both wild-type E coli and strains evolved in the laboratory to be resistant to 23 commonly used antibiotics were analyzed. The researchers performed dose-response experiments to determine the susceptibility of each isolate to a variety of compounds. They then treated those strains with pairs of drugs in a cyclical fashion, such that as the bacteria began to develop resistance to drug A- as measured by the amount of drug it took to inhibit bacterial growth- the team quickly switched to drug B. Later, as the bacteria began to develop resistance to drug B, the researchers applied drug A once more.

The work identified several such sets of antibiotics for which such cycling successfully killed the bacteria without allowing resistance to take hold. Interestingly, they found that drugs belonging to a specific class do not always induce the same effects among the bacteria. As such, the researchers noted that the specific drugs E. coli is exposed to may play a role in determining its sensitivity profile.

This study is an in-depth analysis of resistance linkages and susceptibilities and it's an important topic because development of antimicrobial drugs is expensive and time-consuming, and there aren't very many in the pipeline, so other ways to control resistance are very important.

Still, even if cycling were to improve treatment outcomes, some scientists wonder whether switching up antibiotics can actually help stave off drug resistance in the clinic, or if doing so might contribute to a bigger problem. If the cycling results in an overall reduction in antibiotic usage, resistance rates can go down. But if the cycling results in a reduction in usage of a specific antibiotic as it is replaced by another antibiotic, all that is achieved is replacement of resistance for one drug with another and as soon as the drug that is stopped cycles back on, the resistance comes right back as evidenced by previous clinical data.

Some experts are not convinced that *in vitro* test results are enough to support clinical use of collateral sensitivity cycling at this point and that extensive validation studies are needed. They also added that coming to understand the mechanisms that govern collateral sensitivity will be key. It's important to figure out what makes certain bacteria highly sensitive to some drugs while particularly resistant to others.

References:

1) L. Imamovic, M.O.A. Sommer, Science Translational Medicine, doi: 10.1126/scitranslmed.3006609, 2013.

2) http://www.the-scientist.com/?articles.view/articleNo/37629/title/Giving-Antibiotic-Cycling-Another-Shot/

Global R&D treaty: Boosting innovation and improving the health of the world's poor- and rich

Mounting evidence shows that the existing global system for pharmaceutical research and development (R&D) is badly out of tune with the needs of society. National health systems in the UK and the Netherlands shied away from providing certain recommended medicines due to price. In the US, waiting lists for state HIV drug assistance are lengthening due to the high cost of drugs (frequently more than US$20,000/patient/year - a painful irony as evidence rapidly mounts that earlier treatment of HIV not only benefits the patient, but also reduces the risk of transmission.

Medicine prices are often just as high in developing countries, though incomes are far lower and social safety nets much weaker. Governments, insurers, and households everywhere are struggling to afford new medicines.

At the same time, illnesses that primarily affect populations with little purchasing power, such as Chagas disease, are "neglected" because they offer little return on investment for industry. It is not only diseases of the poor that get neglected, but also those with small patient populations and any other area of research that fails to generate sufficient market returns. Some believe that the R&D system suffers from declining rates of innovation, unaffordable prices for end products, and a misalignment between research investments and the medical needs of society.

No single country can manage this problem alone. Today, research advances produced anywhere can benefit people and contribute to scientific progress everywhere. But financing knowledge production is tricky. Some countries may be tempted to benefit from the knowledge contributed by other countries, but not make commensurate investments. Such "free riding" could, in turn, result in global underinvestment in R&D or limitations on knowledge sharing. A set of rules is needed both to ensure that countries contribute fairly and to create norms and incentives to share knowledge as widely as possible.

In April 2012, a group of international experts convened by the WHO, known as the Consultative Expert Working Group on Research and Development (CEWG), recommended that countries begin negotiations over a binding treaty on medical R&D.

At the moment, the main set of global rules shaping R&D is the 1994 World Trade Organization Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), which requires countries to provide patent protection for drugs and other health technologies. Patents allow pharmaceutical firms to recoup their investments by charging a monopoly price (higher than the cost of production) for new medicines. All countries purchasing patented medicines are thus making contributions towards R&D through these higher prices. But patents are a blunt policy tool: they require trade-offs between innovation and the high prices that restrict patient access to medicines.

A global R&D treaty could encompass a number of measures that would improve the existing system. For example, countries could commit to making sustainable contributions to an international R&D fund. This fund could pay the full costs of R&D so that there would be no need to recoup investments and medicines could be sold at cost, making treatments much more affordable and health systems more sustainable. The system could also drive research into priority diseases, either through traditional grant funding or through novel incentive mechanisms such as prizes for the successful development of products.

Furthermore, the treaty could establish norms for open innovation and create incentives to share research findings quickly in order to accelerate the R&D process. Finally, it could codify obligations for the ethical conduct of clinical trials, which are taking place in more and more countries but may not always be overseen by strong, experienced regulatory institutions. All of these measures are geared toward a global R&D system that would deliver both innovation and equitable access to medicines.

While a treaty won't solve every health challenge or all the woes of industry, building a system of global norms, rules, and incentives that makes public health the key driver of pharmaceutical research would move us towards a more equitable, healthier world.

Source: *http://the-scientist.com/2012/10/01/medicines-for-the-world/*

A phylogenetic study of traditional plant remedies could aid drug development

The medicinal New Zealand flax (Phormium sp.). Phormium species are used traditionally by Māori people to treat a wide range of conditions, including skin, respiratory and gastro-intestinal problems.

A new phylogenetic study suggests that herbal remedies may hold promise for both medicine and drug development. Researchers from the University of Reading in the UK found that many medicinal plants used by nearly 100 cultures on different continents are related. Because these distant groups of people likely identified their plant therapies independently, such herbal treatments may be legitimate, the researchers argue, and the plants likely contain bioactive compounds that scientists could exploit for new drug therapies.

They constructed genus-level phylogenetic trees of plants from 3 dlocations- New Zealand, Nepal, and the Cape of South Africa. Once they assembled their trees, they overlaid ethno-botanical data regarding the therapeutic uses of various plants by cultures from each of the three locations (one culture from New Zealand, three cultures from The Cape of South Africa, and more than 80 cultures from Nepal).

In the flora phylogenies for each of the three continents, medicinal plants clustered into "hot nodes," meaning they were more related to each other than the other plants in the analysis. Further, categorizing medicinal plants by what condition they treated, the researchers found that medicinal plants clustered into condition-specific nodes, even when the analyses from all three locations were combined- again suggesting a high degree of relatedness for plants used to treat similar conditions and lending some validity to these herbal treatments.

Though more than 80% of plant species have not been tested for therapeutic potential, the last major drug discovered from plants was the cancer drug Taxol in 1967.This lack of interest stems, in part, from skepticism about the legitimacy of traditional plant therapies.

Pseudowintera colorata, a plant species used medicinally in New Zealand. Pseudowintera species are used traditionally by Māori people to treat skin conditions, respiratory problems, and to help heal

wounds. Manaaki Whenua Landcare Research, Lincoln, New Zealand, Steven Wagstaff

Another criticism facing the study is that cultures sometimes use symbolic visual cues to identify potentially disease-treating plants. For example, it may be common for traditional healers to treat menstrual symptoms with plants that have red flowers. Such appearance-based selection would suggest that relatedness of medicinal plants is due to looks, not bioactivity.

The researchers also looked at plants being developed or already in use as drug therapies around the globe and found a significant number fell in the nodes with the traditional medicinal plants, further supporting the validity of the method in identifying plants useful for drug discovery. The team noted several plant genera related to traditional medicinal plants that have not been tested for bioactivity, which could serve as low-hanging fruit in the search for new therapies.

Adapted from: *http://the-scientist.com/2012/09/10/rethinking-herbal-medicine/*

IN THE NEWS

Antibiotics linked with increased arrhythmia, death risks

Short-term treatment with the antibiotics azithromycin and levofloxacin may increase the risk of serious cardiac arrhythmias and death.

Previous research has shown a relationship between treatment with azithromycin and an increased risk of cardiovascular death and all-cause mortality in Medicaid patients, especially those at a high risk for cardiovascular disease. These findings led the FDA to issue a public safety warning about the potential risks associated with the antibiotic and similar risks linked with levofloxacin.

Expanding on this research, a study, published in the March/April 2014 issue of the *Annals of Family Medicine*, analysed data from a cohort of veterans treated with azithromycin, levofloxacin, or amoxicillin and evaluated the risks of cardiac arrhythmia and death associated with use of each antibiotic. The analysis included 14 million patients who were treated at 140 Department of Veterans Affairs Medical Centers and 600 outpatient clinics from September 1999 through April 2012.

Azithromycin was typically dispensed for 5 days, while amoxicillin and levofloxacin were generally dispensed for 10 days.

The results indicated that treatment with either azithromycin or levofloxacin was associated with a significant increase in the risk of death and serious arrhythmia. Based on weighted analysis, 228 patients treated with azithromycin and 384 of those treated with levofloxacin per million antibiotics dispensed died after 5 days of treatment, compared with just 154 deaths in patients treated with amoxicillin. At 10 days after the start of treatment, 422 azithromycin patients and 714 levofloxacin patients died per million antibiotics dispensed, compared with 324 amoxicillin patients.

Within the first 5 days of treatment, patients receiving azithromycin had a 48% increased risk of death and a 77% increased risk of serious arrhythmia compared with patients who took amoxicillin. During days 6 to 10 after the beginning of treatment, however, the risk of both death and serious arrhythmia in patients receiving azithromycin were not significantly increased compared with those taking amoxicillin. During the first 5 days of treatment, patients who received levofloxacin had a 149% increased risk of death and a 143% increased risk of serious arrhythmia compared with those who took amoxicillin. The increased risks associated with taking levofloxacin compared with taking amoxicillin remained significantly increased throughout the 10-day treatment period, with the risk of death increased 95% and the risk of serious arrhythmia increased 75%.

The findings support safety announcements from the manufacturer of azithromycin and the FDA, the authors note. They suggest that providers should consider the risks and benefits of the antibiotics before making prescribing decisions.

Adapted from: http://www.pharmacytimes.com/news/Antibiotics-Linked-with-Increased-Arrhythmia-Death-Risks#sthash.Q2RugjLA.dpuf

What not to prescribe: APA list aims to make patients safer

The American Psychiatric Association provides five recommendations for appropriate choice of antipsychotic medications.

On September 20, 2013, the American Psychiatric Association (APA) released a list of specific uses of antipsychotic medications that are common, but potentially unnecessary and sometimes harmful, as part of Choosing Wisely®, an initiative of the American Board of Internal Medicine (ABIM) Foundation. According to experts, the content of this list and all of the others developed through the *Choosing Wisely* effort are helping physicians and patients engage in conversations about what care they need and what can be done to reduce waste and overuse in healthcare system and improve overall health. The APA's list includes the following five recommendations:

1. Don't prescribe antipsychotic medications to patients for any indication without appropriate initial evaluation and appropriate ongoing monitoring.

Metabolic, neuromuscular and cardiovascular side effects are common in patients receiving antipsychotic medications for any indication, so thorough initial evaluation to ensure that their use is clinically warranted, and ongoing monitoring to ensure that side effects are identified, are essential.

"Appropriate initial evaluation" includes the following: (a), thorough assessment of possible underlying causes of target symptoms including general medical, psychiatric, environmental or psychosocial problems; (b), consideration of general medical conditions; and (c), assessment of family history of general medical conditions, especially of metabolic and cardiovascular disorders.

"Appropriate ongoing monitoring" includes re-evaluation and documentation of dose, efficacy and adverse effects; and targeted assessment, including assessment of movement disorder or neurological symptoms; weight, waist circumference and/or BMI; blood pressure; heart rate; blood glucose level; and lipid profile at periodic intervals.

2. Don't routinely prescribe two or more antipsychotic medications concurrently

Research shows that use of two or more antipsychotic medications occurs in 4 to 35% of outpatients and 30 to 50% of inpatients. However, evidence for the efficacy and safety of using multiple antipsychotic medications is limited, and risk for drug interactions, noncompliance and medication errors is increased. Generally, the use of two or more antipsychotic medications concurrently should be avoided except in cases of three failed trials of monotherapy, which included one failed trial of Clozapine where possible, or where a second antipsychotic medication is added with a plan to cross-taper to monotherapy.

3. ***Don't use antipsychotics as first choice to treat behavioral and psychological symptoms of dementia***

Behavioral and psychological symptoms of dementia are defined as the non-cognitive symptoms and behaviors, including agitation or aggression, anxiety, irritability, depression, apathy and psychosis. Evidence shows that risks (e.g., cerebrovascular effects, mortality, parkinsonism or extrapyramidal signs, sedation, confusion and other cognitive disturbances, and increased body weight) tend to outweigh the potential benefits of antipsychotic medications in this population.

Clinicians should limit the use of antipsychotic medications to cases where non-pharmacologic measures have failed and the patients' symptoms may create a threat to themselves or others. This item is also included in the American Geriatric Society's list of recommendations for "Choosing Wisely."

4. Don't routinely prescribe antipsychotic medications as a first-line intervention for insomnia in adults

There is inadequate evidence for the efficacy of antipsychotic medications to treat insomnia (primary or due to another psychiatric or medical condition), with the few studies that do exist showing mixed results.

5. Don't routinely prescribe antipsychotic medications as a first-line intervention for children and adolescents for any diagnosis other than psychotic disorders

Recent research indicates that use of antipsychotic medications in children has nearly tripled in the past 10 to 15 years, and this increase appears to be disproportionate among children with low family income, minority children and children with externalizing behavior disorders (i.e., rather than schizophrenia, other psychotic disorders and severe tic disorders). Evidence for the efficacy and tolerability of antipsychotic medications in children and adolescents is inadequate and there are notable concerns about weight gain, metabolic side effects and a potentially greater tendency for cardiovascular changes in children than in adults.

Sources:

1. *What Not to Prescribe: APA List Aims to Make Patients Safer. Medscape. Sep 20, 2013*
2. *http://www.choosingwisely.org/doctor-patient-lists/american-psychiatric-association/*

STATE OF KUWAIT
Pharmaceutical & Herbal Medicines Control and Registration Administration

New Pharmaceutical products approved from April and May 2015

Altargo Ointment; Retapamulin-10mg; Glaxo Group Ltd.- U.K.
Aragam Soln. for Infn. 2.5g, 5g; Human normal immunoglobulin-2.5g, 5g; Oxbridge Pharma Ltd./U.K.
Aropem Pwdr. For Solution for IV Inj. /Inf. 0.5g, 1g; Meropenem -0.5g, 1g; Arwan Pharm. Ind. Leba non s.a.l- Lebanon
Biscor Tabs. 5mg; Bisoprolol Fumerate-5mg; Pharma Int. Co.-Jordan
Ciazil Soln. for Inj.10mg/ 5ml; Epirubicin HCl-10mg; Genepharm S.A- Greece
Ciazil Soln. for Inj.50mg/ 25ml; Epirubicin HCl-50mg; Genepharm S.A -Greece
Citapram Tabs. 20mg, 40mg; Citalopram - 20mg, 40mg; Pharma Int. Co.-Jordan
Clopidocor Tabs. 75mg; Clopidogrel-75mg; Sandoz Pharm. GmbH-Germany
Clottafact Pwdr. & Solvent for Soln. for Inj. 1.5g/100ml; Human Fibrinogen-1.5g; LFB Biomedicaments -France
Donepezil Orodispersible Tabs. 5mg, 10mg; Donepezil HCl-5mg, 10mg; Genepharm S.A. -Greece
Ebernet Cream 1%; Eberconazole-10mg; Laboratorios Salvat, S.A./Spain
Emipride Tabs. 2mg, 3mg; Glimepiride-2mg, 3mg; Globalpharma Co. LLC-U.A.E.
Emivix Tablets 75mg; Clopidogrel-75mg; Global Pharma Co. LLC- U.A.E.
Esbriet Caps. 267mg; Pirfenidone -267mg; F.H. La Roche Ltd. -Switzerland
Esomeprazol Azevedos Pwdr. For Soln. for Inj. /Inf. 40mg; Esomeprazole-40mg; Lab. Azevedos Indus tria Farmaceutica S.A. - Portugal
Exemestane Genepharm Tabs. 25mg; Exemestane-25mg; Genepharm S.A -Greece
Factane Powd. & Solvent for Soln. for Inj. 1000 IU/5ml; Human coagulation factor VIII -1000 IU Water for Inj. -5ml; LFB -Biomedicaments-France
Factane Powd. & Solvent for Soln. for Inj. 2000 IU/10ml; Human coagulation factor VIII -2000 IU Water for inj.-10ml; LFB -Biomedicaments-France
Folotyn Soln. for Infn. 20mg/ml; Pralatrexate-20mg; Mundipharma Medical Co./Switzerland
Fosrenol Chewable Tabs. - 500mg, 750mg; Lanthanum -500mg, 750mg; Shire Pharm. Contracts Ltd. U.K.
Fycompa Tabs. 2mg, 4mg,6mg, 8mg, 10mg, 12mg; Perampanel-2mg, 4mg, 6mg, 8mg, 10mg, 12mg; EISAI Europe Ltd.- U.K.
Glozimax Capsules 250mg; Azithromycin-250mg; Global Pharma Co. LLC- U.A.E.
Glozimax Powder for Oral Suspn. 200mg/5ml; Azithromycin-200mg; Globalphar ma Co. LLC-U.A.E.
Glozimax Powder for Oral Suspn. 300mg/7.5ml; Azithromycin-300mg; Globalphar ma Co. LLC-U.A.E.
Glozimax Powder for Oral Suspn. 400mg/10ml; Azithromycin-400mg; Globalphar ma Co. LLC-U.A.E.
Incresync Tabs. 25mg/15mg; Alogliptin-25mg, Pioglitazone-15mg; Takeda Pharm. U.S.A. Inc-U.S.A.
Incresync Tabs. 25mg/30mg; Alogliptin-25mg, Pioglitazone-30mg; Takeda Pharm. U.S.A. Inc-U.S.A.
Incresync Tabs. 25mg/45mg; Alogliptin-25mg, Pioglitazone-45mg; Takeda Pharm. U.S.A. Inc-U.S.A.
Insuman Basal Susp. For Inj. 100 IU/ml Inj; Insulin Human -300 IU (rDNA); Sanofi Aventis Deutsch land GmbH/ Germany
Insuman Comb 30 Susp. For Inj. 100 IU/ml; Insulin Human -300 IU (rDNA); Sanofi Aventis Deutschland GmbH/ Germany
Insuman Rapid Soln. For Inj. 100 IU/ml; Insulin Human -300 IU(rDNA); Sanofi Aventis Deutschland GmbH/ Germany
Irbegen Tabs. 150mg, 300mg; Irbesartan-150mg, 300mg; Genepharm S.A. -Greece
Kalpain Soln. for Inf. 10mg/ml; Paracetamol-1000mg; Actavis Group PTC ehf - Iceland
Lady Contraceptive Vaginal Ovules; Nonoxynol 9-120mg; Amcapharm Pharm. GmbH/Germany
Lamepil Tabs. 25mg; Lamotrigine-25mg; IPCA Lab. Ltd.- India
Lebacef Pwdr. & Solvent for IM Injectable 0.5g; Ceftriaxone -0.5g, Lidocaine HCl (1%) 2ml; Arwan

Pharm. Ind. Lebanon s.a.l- Lebanon
Lebacef Pwdr. & Solvent for IM Injectable Soln.1g; Ceftriaxone -1g, Lidocaine HCl (1%)-3.5ml; Arwan Pharm. Ind. Lebanon s.a.l- Lebanon
Lebacef Pwdr. & Solvent for IV Injectable Soln. 1g,Ceftriaxone -1g, 2g, Water for Injection 10ml; Arwan Pharm. Ind. Lebanon s.a.l- Lebanon
Lebacef Pwdr. & Solvent for IV Injectable Soln. 0.5g; Ceftriaxone -0.5g, Water for Injn.-5ml; Arwan Pharm. Ind. Lebanon s.a.l- Lebanon
Levotab Tablets 500mg; Levofloxacin-500mg; Globalphar ma Co. LLC-U.A.E.
Likacin Soln. for IM/IV Inj. 250mg and 500mg/2ml; Amikacin-250mg, 500mg; Lab. Italiano Biochimico Farmaceutico Lisapharma S.p.A/Italy
Mabthera Soln. for subcutaneous Injn. 1400mg/11.7ml; Rituximab (rDNA)-1400mg; F. Hoffmann-La Roche Ltd.- Switzerland
Miran Pwd. For Injn. 1g; Meropenem-1g; Julphar - U.A.E.
Miran Pwd. For Injn. 500mg; Meropenem-500mg; Julphar -U.A.E.
Mofilet Tablets 500mg; Mycophenolate Mofetil-500mg; Emcure Pharm. Ltd./India
Myora Tabs. 500mg; Mycophenolate Mofetil-500mg; APM Co. Ltd,/Jordan
Myozyme Pwd. For Conc. For Soln. for Inf.50mg; Alglucosidase Alfa (rDNA)-50mg; Genzyme Europe B.V. /The Netherlands
Norgesic Tablets; Paracetamol-450mg, Orphenadrine Citrate-35mg; Meda Pharmaceuticals S.A. / Greece
Normigore Tabs.75mg; Clopidogrel-75mg; Arwan Pharm. Ind.- Lebanon s.a.l- Lebanon
NovoMix 50 and 70 Penfill Suspn. For Inj; 100 U/ml (cartridge) Insulin Aspart Biphasic (rDNA)-100U; Novo Nordisk A/S / Denmark
Octaplex Pwdr. & Solvent for Soln. for Inf. 500 IU; Multi ingredients; Octapharma Pharmazeutika Produktikonsges m.b.H- Austria
Omeprazol Azevedos Pwdr. For Soln.for Inj./Inf. 40mg; Omeprazole-40mg; Lab. Azevedos Industria Farmaceutica S.A. - Poartugal
Pantoprazol Azevedos Pwdr. For Soln. for Inj/Inf. 40mg; Pantoprazole-40mg; Lab. Azevedos Industria Farmaceutica S.A. - Poartugal
Paraconica IV Soln. for Infn. 1000mg; Paracetamol-1.0g; S.M. Farmaceutici Srl-Italy
Parafusiv Soln. for IV Injn.10mg/ml; Paracetamol-1000mg; Pharma Bavaria Int.- Portugal
Prolax ER Capsules 15mg, 30mg; Cyclobenzaprine HCl-15mg, 30mg; Tabuk Pharm. Mfg. Co./KSA
Resincalcio Pwdr. For Oral Suspn; Calcium Polystyrene Sulphonate-99.75g; Laboratorios Rubio S.A.- Spain
Rinalgit Tabs.10mg; Cetirizine Dihydrochloride-10mg; ABC Farmaceutica S.p.A- Italy
Rivetal Capsules 1.5mg, 3mg, 4.5mg, 6mg; Rivastigmine-1.5mg, 3mg, 4.5mg, 6mg; Genepharm S.A./ Greece

Answers to: Test your knowledge

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

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